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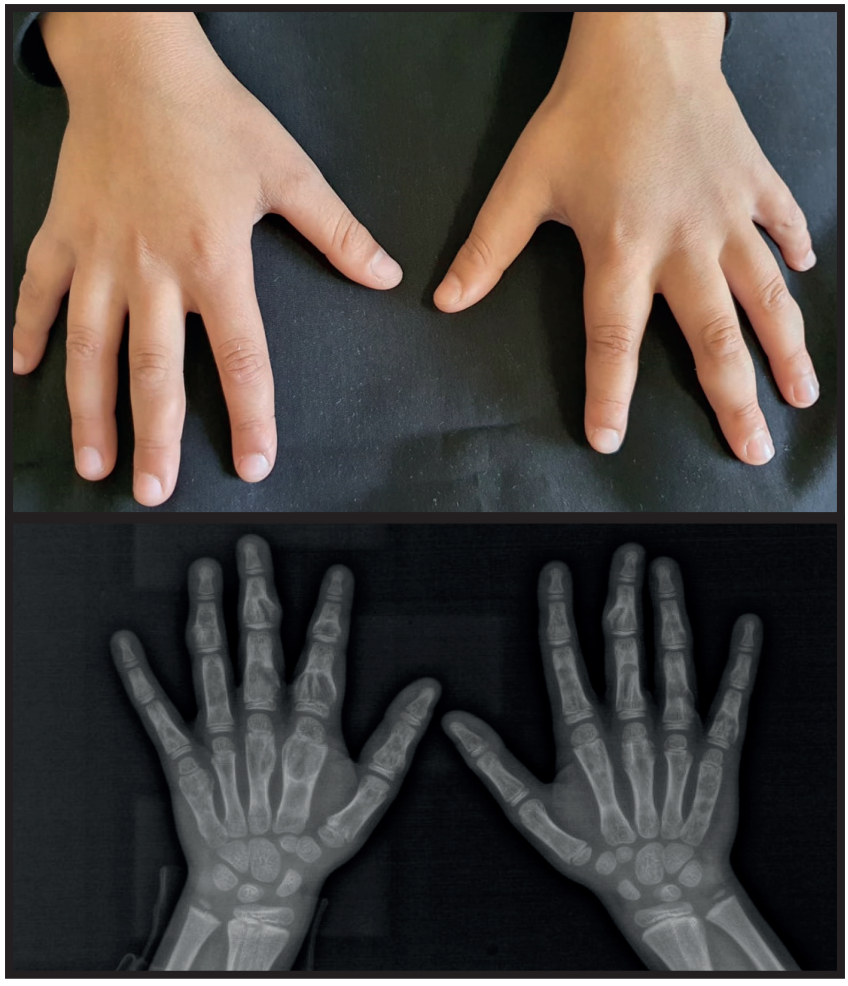

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Review

# Interpretation, differential diagnosis, and clinical implications of abnormal thyroid function tests in children

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## ABSTRACT

In children, abnormal thyroid function tests (TFTs) can present diagnostic difficulty due to the variety of clinical manifestations that may accompany them. Pediatric patients with abnormal TFTs are discussed in this article, along with their differential diagnoses and approaches to management. The most prevalent causes of pediatric hypothyroidism and hyperthyroidism, including Hashimoto's thyroiditis and Graves' disease, are thoroughly reviewed. Additionally, we explore other potential etiologies of abnormal TFTs in children: congenital hypothyroidism, resistance to thyroid hormone, nonthyroidal illness syndrome, medication use, iodine deficiency, and interferences with thyroid function immunoassays. In the setting of the pediatric population, diagnostic assessment and analysis of TFTs involving thyroid-stimulating hormone (TSH), free thyroxine (fT4), and free triiodothyronine (fT3) are addressed.

**Keywords:** Free thyroxine, free triiodothyronine, hyperthyroidism, hypothyroidism, pediatric, thyroid-stimulating hormone, thyroid function tests

## INTRODUCTION

Thyroid function tests (TFTs) are utilized to assess thyroid gland function and establish a diagnosis of thyroid disorders.[1,2] The diagnosis of hyperthyroidism or hypothyroidism based on TFTs is often uncomplicated for clinicians in circumstances where a strong clinical suspicion of thyroid dysfunction exists. However, there are also subclinical forms of thyroid disorders that can manifest as slight alterations in TFTs and situations characterized by inconsistencies between thyroid-stimulating hormone (TSH) and thyroid hormone (TH) levels. The difficulty in diagnosis associated with subclinical and atypical presentations of thyroid disorders highlights the importance of meticulous interpretation of TFT results and consideration of additional diagnostic measures, including specialized laboratory examinations, radiological tests, and, on occasion, genetic analyses.[3]

The purpose of this review is to provide a comprehensive overview of the etiology, clinical manifestations, and management strategies for pediatric patients presenting with abnormal TFTs.

### Thyroid Physiology

The thyroid gland plays a pivotal role in maintaining physiological homeostasis in humans. The hypothalamic-pituitary-thyroid (HPT) axis regulates the production and secretion of THs. The hypothalamus synthesizes thyrotropin-releasing hormone (TRH), which stimulates the anterior pituitary gland to release TSH. Subsequently, TSH stimulates the production of 3,3',5,5'-tetraiodothyronine (thyroxine, T4) and 3,3',5-triiodothyronine (T3).[4-6]

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T4 is the predominant form of TH that is secreted by the thyroid gland, accounting for roughly 85-90% of the total TH stored in the gland. The remaining 10-15% of stored TH is T3, the biologically active form of TH, which is mainly produced by converting T4 in the peripheral tissues through the action of deiodinases. Over 99% of circulating T4 and T3 are bound tightly to carrier proteins, including thyroid hormone-binding globulin (TBG), albumin, and transthyretin. The carrier-bound hormone primarily serves as a reservoir, whereas the unbound fractions, referred to as free T4 (fT4) and free T3 (fT3), enter the cells and employ their physiological actions. Additionally, both fT4 and fT3 play a crucial role in the negative feedback inhibition of TRH and TSH secretion, respectively.[4,7,8]

In order for THs to exert their genomic effects, they need to be carried into the cells and subsequently bind to nuclear receptors. The THs require transmembrane protein transporters to access specific types of cells. These transporters encompass monocarboxylate transporters 8 and 10 (MCT8 and MCT10), organic anion transporters (OATPs), and L-amino acid transporters (LATS).[4,9,10] Once inside the cell, the activity of THs depends on various deiodinases, which are selenoproteins expressed differently in diverse cell types. Specific deiodinases in the bloodstream and target cells convert T4 to active T3 and inactive 3,3',5'-triiodothyronine (reverse T3, rT3).[4,9]

Most biological activities of TH are mediated by the binding of T3 to nuclear T3 receptors (TRs). The two thyroid receptor genes *THRA* and *THRB* encode TH receptor-α (TRα) and TH receptor-β (TRβ), respectively. These genes lead to the production of three TRα and three TRβ isoforms. TRα1, TRβ1, and TRβ2 are the isoforms that bind to T3. TRα1 primarily in the brain, heart, and bone, and TRβ1 primarily in the liver, kidney, and thyroid. TRβ2 has a more limited expression pattern but is the predominant isoform expressed in the pituitary gland and is thus critical for the negative regulation of TSH.[4,9,11-13]

**Thyroid-Stimulating Hormone (Thyrotropin, TSH)**

TSH is a hormone that plays a crucial role in regulating thyroid gland function. It is produced by the anterior pituitary gland and acts on the thyroid gland to stimulate the production and release of THs. TSH is controlled by a feedback mechanism that involves the hypothalamus and the thyroid gland. When the levels of THs in the blood are low, the hypothalamus releases TRH, which stimulates the pituitary gland to release TSH. In turn, TSH stimulates the thyroid gland to produce and release more THs, which helps raise the levels of THs in the blood.[5,8] TSH secretion is very sensitive to even minor changes in TH levels. Specifically, the relationship between TSH and free TH is characterized as being inversely log-linear. This suggests that even small reductions in fT4 levels can result in a substantial exponential increase in TSH secretion.[3]

TSH secretion exhibits a circadian pattern, with its highest levels typically observed in the early hours of the morning. Studies have demonstrated that TSH concentrations can differ by as much as 2 mIU/mL between morning and evening measurements. As a result, it is advised to perform TSH assessments in the morning and to repeat measurements if necessary.[2] Additionally, It is important to acknowledge that when interpreting TSH levels in children, it is necessary to take into account that the normal range is not the same as that of adults, in whom the upper limit value is approximately 4 μU/mL or lower.[8]

**Thyroxine (total T4 and free T4)**

T4 is the major hormone produced by the thyroid gland. T4 is formed through the merging of two diiodothyronine (DIT) molecules. T4 is synthesized and secreted into the circulation in response to TSH released from the pituitary gland. T4 binds to transport proteins such as TBG, albumin, and transthyretin, which prevent its clearance and facilitate its distribution throughout the body. Once T4 enters cells, it undergoes deiodination to produce the active hormone T3, which binds to nuclear THRs to modulate gene expression and cellular metabolism.[8]

Abnormal levels of T4 can lead to significant physiological changes in the body. Hypothyroidism, a condition characterized by decreased thyroid hormone production, is commonly associated with low T4 levels. Conversely, hyperthyroidism, a condition characterized by increased thyroid hormone production, is commonly associated with high T4 levels.[2,3]

Assessment of T4 levels is an important diagnostic tool for the evaluation of thyroid function. Measurement of total T4 levels was commonly used in clinical practice, but fT4 levels, which represent the unbound, biologically active form of the hormone, provides more accurate reflection of thyroid status. Additionally, measurement of fT4 levels in combination with TSH levels aids in the differential diagnosis of primary and secondary thyroid dysfunction.[3,7,8]

**Triiodothyronine (total T3 and free T3)**

T3 is the bioactive TH that is essential for normal growth and development. Like T4, the production of T3 is regulated by the hypothalamus and pituitary. T3 is formed by the conversion of T4 in various tissues through the action of the enzyme deiodinase.[8] Type 2 deiodinase generates T3 through the outer ring deiodination process of T4. Conversely, type 3 deiodinase performs inner ring deiodination, which results in

the inactivation of T3 by converting it into 3,3'-diiodothyronine (T2) or inhibiting T3 synthesis from T4 by converting T4 to rT3. Type 1 deiodinase, depending on the substrate, carries out inner or outer ring deiodination, leading to the generation of T3, rT3, or T2.[5]

Measuring T3 in most clinical situations is unnecessary, and it should not be included as part of the initial screening for thyroid dysfunction. T3 measurements are only appropriate in certain clinical circumstances. If the clinical concern is primary hypothyroidism, T3 measurements should not be done as a routine test. T3 levels remain normal in primary hypothyroidism because of the increase in peripheral deiodinases and optimal thyroid stimulation resulting from elevated TSH levels.[2,3] fT3 measurements should only be carried out in patients suspected to have hyperthyroidism or in certain diseases among the group of impaired sensitivity to THs.[14]

## DIAGNOSTIC APPROACH TO ABNORMAL THYROID FUNCTION TESTS

In Figure 1, a general approach based on fT4 is presented. Certain conditions or diseases may be found in multiple subgroups. Table 1 shows typical TFT findings of major diseases classified according to TSH levels.

**Table 1. A summary of the conditions primarily classified to typical TSH levels**

| | fT4 | fT3 | Thyroid status | Additional clinical and biochemical features |
|---|---|---|---|---|
| ***Low TSH*** | | | | |
| **Graves' Disease** | High | High | Hyperthyroid | Eye disease, goitre, anti-TSH receptor antibody |
| **Neonatal thyrotoxicosis** | High | High | Hyperthyroid | Anti-TSH receptor antibody |
| **Hashitoxicosis** | High | High | Hyperthyroid | |
| **Euthyroid sick syndrome** | Normal/Low | Low | Euthyroid | High serum rT3 |
| **Biotin interference** | High | High | Euthyroid | Symptoms of hyperthyroidism lacking |
| **Central hypothyroidism** | Low | Low/Normal | Hypothyroid | TSH levels may be normal, low, or mildly high |
| ***High TSH*** | | | | |
| **Congenital or acquired hypothyroidism** | Low/Normal | Normal | Hypothyroid/ Euthyroid | Additional features according to underlying pathology |
| **Subclinical hypothyroidism** | Normal | Normal | Euthyroid | Hashimoto's thyroiditis, obesity, trisomy 21 |
| **TSHoma** | High | High | Hyperthyroid | High levels of the alpha-glycoprotein subunit |
| ***Normal TSH*** | | | | |
| **Resistance to thyroid hormone β** | High | High | Euthyroid/ Hyperthyroid | High rT3<br>Generally asymptomatic, growth retardation, failure to thrive, goiter, tachycardia |
| **Resistance to thyroid hormone α** | Low or lower half of normal range | High or upper half of normal range | Hypothyroid | Constipation, short stature, motor retardation, speech delay, bradycardia |
| **MCT8 Deficiency** | Low or lower half of normal range | High or upper half of normal range | Cerebral hypothyroidism with peripheral hyperthyroidism | Low rT3, and normal or slightly elevated levels of TSH<br>Developmental delay, hypotonia, poor weight gain, feeding difficulties, tachycardia |

*TSH, thyroid-stimulating hormone; fT4, free thyroxine; fT3, free triiodothyronine; rT3, reverse triiodothyronine; TG, thyroglobulin; TPO, thyroperoxidase; MCT8, monocarboxylate transporters 8

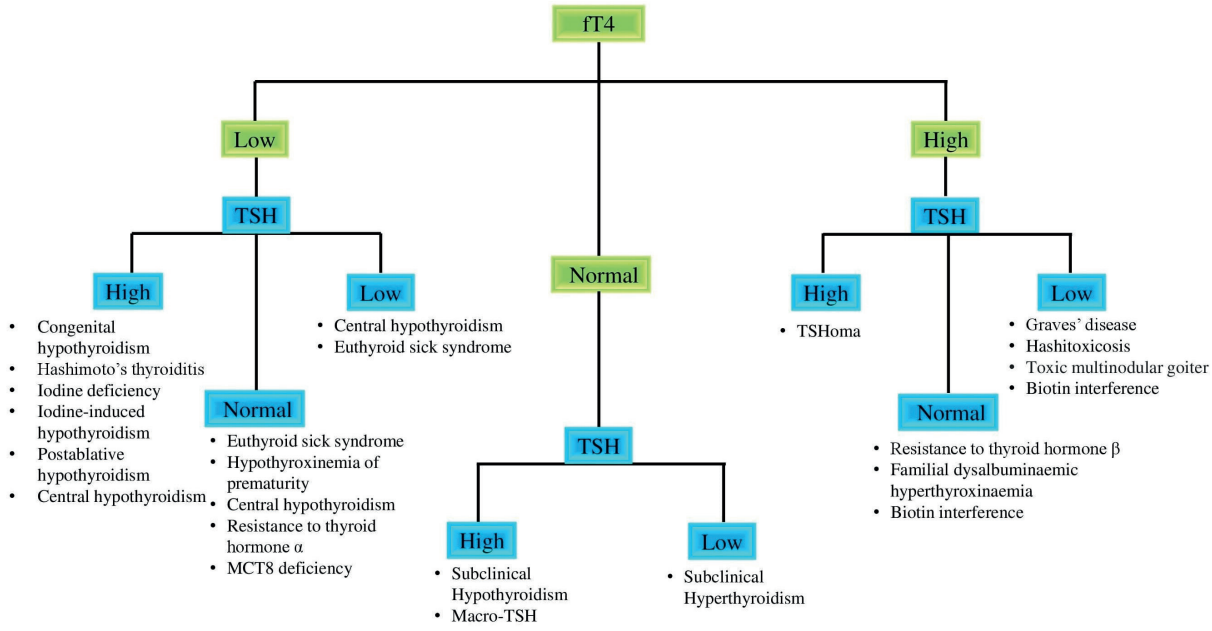


**Figure 1.** A general approach based on fT4

### Low Free T4 Levels

Low levels of THs in the bloodstream can arise from dysfunction anywhere in the HPT axis. Hypothyroidism can manifest either at birth or develop later in life. It can result from intrinsic defects in the thyroid gland, leading to inadequate production of THs. Additionally, hypothyroidism can be of central origin, resulting from reduced secretion of TSH or TRH. Furthermore, abnormalities in TH transport or action can also be associated with low levels of T4.

### 1. Congenital Hypothyroidism

Congenital hypothyroidism (CH), the commonest neonatal endocrine condition, results from a deficiency of TH production during fetal development. The incidence of CH varies depending on the geographical region, ranging from 1 in 2.000 to 1 in 3.000 live births worldwide. Primary CH can result from developmental abnormalities of the thyroid gland (thyroid dysgenesis) or congenital defects in TH production (dyshormonogenesis). Thyroid dysgenesis is the primary cause of CH, accounting for approximately 80% to 85% of all cases, followed by thyroid dyshormonogenesis. CH can be transient due to reasons linked to the mother or newborn, and the leading cause is an iodine deficiency. Additionally, iodine excess can also lead to transient primary CH through the Wolff-Chaikoff effect. It can also effect newborns via breastfeeding (povidone-iodine douching or iodine-containing tampons for episiotomy antisepsis after vaginal delivery). Furthermore, transient CH may be caused by the transplacental transfer of maternal antithyroid drugs, transplacental transfer of maternal TSH-receptor blocking IgG antibodies, and DUOX2 mutations.[1,5,8]

It is very important to diagnose and treat CH as soon as possible in early life to ensure normal cognitive and developmental abilities.[1,15] The primary method for detecting CH is newborn screening, which mainly involves measuring TSH levels in capillary whole blood within a few days of birth. In many countries, newborn screening programs for CH have been established as a standard of care, enabling early detection and timely intervention for affected infants.[16] The newborn screening for the diagnosis of CH was initially introduced in both Quebec, Canada, and Pittsburgh, Pennsylvania, in 1974.[17] The optimal approach for performing and optimizing newborn screening for congenital hypothyroidism remains a topic of debate. Essentially, two screening methods are commonly employed: (i) screening with TSH measurement (T4 measurement as required) and (ii) screening with T4 measurement (TSH measurement as required).[15] As of 2006, national screening began in Turkey, utilizing a method based on TSH measurement from blood samples collected by heel-prick and blotted on filter paper (the "Guthrie card").[18]

Certain groups of children with delayed TSH elevation, such as preterm infants, low-birth-weight newborns, and sick preterm infants who are hospitalized in neonatal intensive care units, may receive neonatal screening results that incorrectly indicate they are healthy, or the results may miss mild cases of CH. In

such instances, a post-screening plan that involves collecting a second specimen at 14 days of age or 2 weeks after the initial test may be considered.[15,18]

Newborns who have a positive result on the screening test should undergo clinical evaluation and venous measurements of fT4 and TSH. To ensure prompt administration of necessary treatment, this evaluation should occur within 24 hours of referral. The diagnosis of CH in infants should be based on low serum fT4 levels for age, and TH therapy should be initiated immediately. Etiological investigations should not delay treatment. Measuring serum TH levels is recommended in infants presenting clinical symptoms of hypothyroidism, even if their screening results are normal.[5,15,18]

CH is confirmed when venous fT4 is below the reference range and/or venous TSH is >20 mU/L. In instances where the fT4 is within normal limits and the TSH is between 6 and 20 mU/L beyond 21 days of age, it is recommended to repeat testing and utilize clinical judgment. Typically, the TSH level tends to decrease spontaneously within the normal range. However, if the fT4 level declines or the TSH level remains persistently elevated, initiating levothyroxine therapy is likely to be necessary. It is crucial not to defer treatment initiation while waiting for test results, particularly if the TSH level in the screening whole blood sample exceeds 40 mU/L.[15] It should be noted that in order to calculate approximate serum equivalent, capillary TSH levels should be multiplied by 2.2.[19] Moreover, when the serum fT4 level is low and the TSH level is low, normal, or slightly elevated, the diagnosis of central CH must be considered.[5,15]

**2. Hypothyroxinemia of Prematurity**

Hypothyroxinemia of prematurity (HOP) is a common condition that affects up to 50% of infants born before 28 weeks of gestation and is related to the immaturity of the HPT axis. It is usually transient and resolves within the first few weeks of life, and is characterized by low levels of T4 with normal TSH. As gestational age decreases, thyroxine concentrations in infants become progressively lower normally. Low concentrations of fT4 may serve as an indicator of illness severity or possibly as a protective mechanism to decrease metabolic rate.[5,8]

There are several risk factors that have been identified in studies for this abnormality, including lower gestational age, maternal pre-eclampsia, respiratory distress syndrome, mechanical ventilation, and dopamine infusions. Besides, preterm infants may experience iodine deficiency as a result of inadequate levels in parenteral nutrition and the rapid loss of maternal supply, which can impede recovery from hypothyroxinemia of prematurity. As a consequence, exposure to excessive iodine from sources such as disinfectants or radiological contrast infusions can lead to a decrease in T4 and T3 levels, a phenomenon referred to as the Wolff-Chaikoff effect.[20]

The optimal management of HOP is still a matter of debate, and there is currently no consensus on the best treatment approach for HOP. Close monitoring of TH levels is essential to identify infants who may benefit from treatment. Work up for other pituitary hormones may be performed in order to exclude or confirm central hypothyroidism. Further research is needed to determine the optimal management of HOP and to improve the long-term outcomes of premature infants affected by this condition.[21-23]

**3. Acquired Primary Hypothyroidism**

The most prevalent cause of acquired hypothyroidism in children and adolescents worldwide is severe iodine deficiency, but in areas where iodine is sufficient, it is more frequently caused by chronic autoimmune thyroiditis, also known as Hashimoto's thyroiditis.[13,24] Acquired hypothyroidism can also occur due to other, less common etiologies. For instance, the chronic administration of high doses of iodine from iodinated contrast material, the highly iodinated antiarrhythmic amiodarone, the topical antiseptic povidone-iodine, or iodine-containing thyroid supplements may result in hypothyroidism.[1,5,13] In addition, acute thyroiditis, radiation therapy to the head and neck for certain cancers, total-body irradiation before a bone marrow transplant, as well as several medications, such as lithium.[1]

**a. Hashimoto's Thyroiditis (Autoimmune Thyroiditis)**

Hashimoto's thyroiditis is an autoimmune disorder that affects the thyroid gland, causing it to become inflamed and unable to produce sufficient THs. Although it is more commonly seen in adults, Hashimoto's thyroiditis is the most common acquired thyroid disease in childhood, with an estimated incidence of 1 to 2 cases per 1000 children.[1] Hashimoto's thyroiditis is a condition characterized by the presence of antibodies against thyroglobulin (TG) and thyroperoxidase (TPO), leading to infiltration of the thyroid gland with lymphocytes and subsequent enlargement. Depending on the specific antithyroid antibodies involved, Hashimoto's disease may lead to a euthyroid state, hypothyroidism, or transient hyperthyroidism. The condition typically presents in adolescents and is more prevalent among females than males. Furthermore, Hashimoto's thyroiditis is more commonly seen in patients with type 1 diabetes mellitus, celiac disease, vitiligo, alopecia, rheumatoid arthritis, Down syndrome, Turner syndrome, Klinefelter syndrome, autoimmune polyglandular syndrome, and IPEX (immunodysregulation polyendocrinopathy enteropathy X-linked) syndrome.[5,8]

Confirmation of hypothyroidism due to Hashimoto's thyroiditis involves elevated TSH, low fT4, the presence of TPO or TG antibodies, and/or a characteristic ultrasound appearance. However, in some cases of Hashimoto's thyroiditis, the goiter may be the only presenting feature, and half of the children at the time of diagnosis may have normal thyroid function. Children who are younger or have Down syndrome or Turner syndrome are more likely to have abnormal thyroid function at the time of diagnosis.[25]

**b. Iodine Deficiency**

Iodine is an essential micronutrient required for the synthesis of THs, and insufficient dietary intake of iodine may result in hypothyroidism. Inadequate iodine intake is prevalent among people residing in iodine-deficient areas. In developed countries, inadequate dietary intake may arise from self-imposed restrictions on iodized salt consumption, prolonged parenteral nutrition without iodine supplementation, and the use of enteral formulas with low iodine concentration.[26,27] In children and adolescents with iodine deficiency, thyroid function is characterized by a high fT3, low fT4, and a normal or slightly elevated TSH, in addition to high TG levels.[28]

**c. Iodine-Induced Hypothyroidism**

Sufficient iodine intake is necessary for proper thyroid function, but excessive iodine exposure can result in a rapid decline in the release of preexisting TH and hindered TH synthesis, which is referred to as the Wolff-Chaikoff effect. Several factors may lead to excessive iodine intake, including excess consumption of nutritional supplements and cough suppressants containing high amounts of iodine, the use of radiocontrast dyes, amiodarone, and iodinated antiseptics. Moreover, individuals living in iodine-deficient areas may be at increased risk of iodine-induced hypothyroidism due to sudden exposure to high levels of iodine.[29] The diagnosis of iodine-induced hypothyroidism is based on abrupt onset and demonstration of of elevated urinary iodine levels.[5,8]

**d. Postablative Hypothyroidism**

Annual TSH screening is recommended for up to 30% of children who have received irradiation to the head and neck area, as they are at risk of developing primary hypothyroidism in the long-term follow-up. Furthermore, postablative hypothyroidism can occur as a consequence of subtotal or total thyroidectomy or radioactive iodine therapy.[8,28]

**4. Euthyroid Sick Syndrome (Nonthyroidal Illness or Low T3 Syndrome)**

Low fT3 and fT4 along with normal TSH levels can be associated with various moderate to severe non-thyroidal factors, such as the neonatal period, stress, cold exposure, infection, calorie deprivation, surgery, medications (such as propranolol, amiodarone, and diphenylhydantoin), hepatic dysfunction, and renal dysfunction.[28] During critical illness, there is a tendency for T4 to convert into the metabolically inert rT3 instead of the biologically active form, T3. This mechanism serves as a protective response by reducing metabolic demands and conserving energy. Subsequently, fT4 levels also decrease, accompanied by a decline in TSH levels. As the individual recovers, there is an initial increase in TSH levels, which may occasionally exceed the normal range. Eventually, the free TH levels normalize, indicating the restoration of thyroid function.[3] Treatment of euthyroid sick syndrome primarily focuses on addressing the underlying illness rather than directly targeting the TH abnormalities. Administering TH treatment is unnecessary and may have adverse effects that outweigh any potential benefits.[5,28,30]

**5. Central Hypothyroidism**

Central hypothyroidism is a rare cause of hypothyroidism, accounting for less than 1% of all cases. It may be secondary due to inadequate secretion of TSH from the pituitary gland or tertiary due to inadequate secretion of TRH from the hypothalamus. Central hypothyroidism can be congenital due to various genetic alterations or acquired particularly due to tumors or irradiation.[8,28] Central hypothyroidism can be associated with other pituitary hormone deficiencies. In cases where infants have multiple pituitary hormone deficiencies, they may experience symptoms such as hypoglycemia, cholestatic jaundice, micropenis, and cryptorchidism.[1,5]

In contrast to primary hypothyroidism, diagnosing central hypothyroidism can be challenging. Typically, fT4 levels are low while TSH levels may be normal, low, or slightly high.[5,31] On the other hand, despite being in normal range, progressive decline in fT4 levels to lower quartile of reference range in a patient with known hypothalamopituitary dysfunction suggest central hypothyroidism.[32]

**6. Disorders of Thyroid Hormone Transport: MCT8 Deficiency**

TH transporter proteins on the plasma membrane play a crucial role in regulating the intracellular availability of THs. Among the identified TH transporters, monocarboxylate transporter

8 (MCT8; solute carrier family 16A2, *SLC16A2*) stands out as one of the most efficient and specific transporters known to date. MCT8 facilitates the cellular uptake and release of T3, T4, and the inactive metabolite rT3. This protein exhibits wide expression in various tissues, with prominent thyroid, liver, kidney, and brain localization.[33,34] MCT8 deficiency, also known as Allan-Herndon-Dudley syndrome, is a rare and severe disorder that is characterized by neurological and metabolic consequences. It is caused by pathogenic variants in the *MCT8* gene and has an estimated prevalence of 1 in 70,000 males.[35] The malfunctioning MCT8 disrupts the homeostasis of THs in the brain, consequently causing neurodevelopmental delay due to cerebral hypothyroidism. However, the elevated levels of circulating T3 concentrations cause thyrotoxicosis in MCT8-independent tissues.[34]

The thyroid biochemistry observed in individuals with MCT8 deficiency is characterized by significantly elevated levels of fT3 (rarely in the upper half of normal), decreased levels of fT4 (either low or within the lower end of the normal range), reduced levels of rT3, and normal or slightly elevated levels of TSH. The majority of patients exhibit elevated serum concentrations of SHBG, indicating the hepatic action of thyroid hormones. Conversely, serum concentrations of creatine kinase (CK), reflecting thyroid hormone action in muscles, are frequently observed to be low within the normal reference range.[34] Brain magnetic resonance imaging scanning reveals a global delay in myelination that improves with age. Additionally, diffuse atrophy is present with concomitant ventricle dilatation.[36]

**7. Resistance to Thyroid Hormone α (RTHα)**

TRα-mediated RTH is caused by heterozygous, dominant-negative, loss-of-function mutations in the *THRA* gene.[5] This condition manifests varying degrees of symptoms similar to that of primary hypothyroidism. However, the TFTs of affected individuals are near normal due to intact TRβ, which regulates the negative feedback of THs in the hypothalamus and pituitary glands.[11]

Typically, TSH levels are normal, fT4 slightly low or in the lower half of normal range, and fT3 slightly high or at the upper half of normal range, leading to an abnormally low T4/T3 ratio. Additionally, affected individuals commonly present with mild normocytic anemia and elevated levels of muscle CK.[12,37] Diagnosis is important since clinical picture ameliorates with levothyroxine treatment in most of the patients.[12]

**High Free T4 Levels**

Elevated serum levels of TH mostly indicate inappropriately increased production or secretion of TH to bloodstream. In this case TSH levels are suppressed. On the other hand, in some cases there is an abnormality in TH metabolism or fT4 levels are falsely found elevated due to interference.

**1. Graves' Disease**

Graves' Disease (GD) is the most common cause of hyperthyroidism in children, accounting for more than 95% of cases, and the incidence is between 1 and 3/100,000. The onset of GD can occur at any stage of childhood, but its prevalence increases with age and peaks during adolescence. The frequency of GD is higher in children with other autoimmune conditions as well as with some syndromes such as Down syndrome and Turner syndrome, and in children with a family history of autoimmune thyroid disease.[5,38]

GD occurs as a result of the production of TSH receptor-stimulating immunoglobulins (TSIs), which are antibodies that activate the TSH receptor on thyroid follicular cells. These TSIs were previously known as long-acting thyroid stimulators and stimulate increased vascularity, follicular hypertrophy and hyperplasia, and excessive synthesis and secretion of THs. This, in turn, leads to diffuse thyroid enlargement and the development of a palpable goiter. Along with TSIs, the body produces neutral and inhibitory thyroid antibodies, whose levels and affinity to the TSH receptor can change, resulting in variations in TH levels and clinical symptoms.[38,39]

When hyperthyroidism is suspected, it is recommended to measure the levels of fT3, fT4, TSH and thyroid autoantibodies, including anti TPO (anti- thyroperoxidase ), antiTG (anti-thyroglobulin ), and TRAbs (TSH receptor antibodys, preferably TSIs). GD is characterized by increased production of T3 and T4, an increased T3/T4 ratio, and a suppressed TSH level. Unlike the assessment for hypothyroidism, it is crucial to include the measurement of T3 levels in the evaluation for GD since an isolated rise in T3 levels may occur before a rise in T4 levels in the early stages. If clinical presentation suggests GD but thyroid antibodies are not detected, it is recommended to repeat the antibody tests after a few weeks.[1,5,40] If there is still no evidence of thyroid autoimmunity, further investigations such as thyroid ultrasonography, scintigraphy (preferably using Tc-99m-pertechnetate), and additional laboratory tests may be considered.[41]

**2. Neonatal Thyrotoxicosis**

Neonatal thyrotoxicosis is predominantly caused by maternal TRAbs that cross the placenta, leading to neonatal GD. Although this condition is generally temporary and self-limiting, it can result in severe clinical manifestations and long-term complications as well. Neonatal thyrotoxicosis occurs in 1% to 5% of infants born to affected mothers, resulting in an estimated incidence of neonatal GD of 1 in 25,000 neonates.[40] Rarely neonatal thyrotoxicosis will persist, like the GD disease seen in older children.[8] TFTs and TRAbs should be performed on neonates born to mothers with a history of GD (either active or in the past). If neonatal thyrotoxicosis is diagnosed, treatment should be initiated promptly.[18,40] Rarely, activating mutations of TSH receptor gene (TSHR) can lead to neonatal onset hyperthyroidism, in such cases autoimmune markers are negative.[42,43]

**3. Hashitoxicosis**

Hashitoxicosis, a transient phase of autoimmune thyroiditis, can occur due to the release of stored T4 and T3 from the damaged thyroid gland. The duration of the hyperthyroid phase may last for several weeks to months, and its associated symptoms can be managed with beta-blockers. Unlike GD, there are no eye-related symptoms, and there is no elevation of TSIs.[44] Thyroid scintigraphy can be used to determine the underlying pathology, which is characterized by increased uptake due to TSH receptor stimulation in GD and reduced uptake in hashitoxicosis.[45] Hashitoxicosis typically resolves spontaneously, and consequently, the child may develop hypothyroidism in the future. Therefore, close monitoring of thyroid function is essential.[5]

**4. McCune–Albright Syndrome**

McCune-Albright syndrome is a genetic disorder characterized by spontaneous activation of the alpha subunit of the G protein. Because the TSH receptor is G protein-coupled, somatic mutations of the alpha subunit within the thyroid gland may result in hyperthyroidism. The somatic mutations associated with this condition can also cause various simultaneous endocrine disorders, such as Cushing syndrome, precocious puberty, and growth hormone excess. It is often accompanied by characteristically large café au lait skin pigmentation and polyostotic fibrous dysplasia. Nodular goiter, which is associated with thyroid hyperfunction, can develop at any age, including during the neonatal period. Autoimmune markers are negative. In addition to the excessive production of fT4 due to TSH-independent stimulation, there is also evidence of intrathyroidal deiodinase type 1 and 2 overactivity, which results in an elevated T3/T4 ratio.[46,47]

**5. TSH-Secreting Pituitary Adenoma (TSHoma)**

TSHoma is a rare type of pituitary tumor that causes hyperthyroidism by producing excessive TSH. These tumors are usually characterized by macroadenomas. Elevated levels of THs and TSH are common in TSHoma. It is important to distinguish TSHoma from resistance to thyroid hormone β (RTHβ), which can have similar biochemical features. Notable distinguishing features of TSHoma include clinically apparent thyrotoxicosis, pituitary tumor, non-responsiveness to TRH stimulation, and elevated levels of the alpha-glycoprotein subunit.[48]

**6. Toxic Multinodular Goiters**

Toxic multinodular goiter (TMNG) is rare in children; however, affected patients may develop thyrotoxicosis, which is typically correlated with the duration and size of the goiter. In this context, hyperthyroidism occurs when a nodule within the thyroid becomes hyperactive and functions autonomously.[49]

**7. Biotin Interference**

Biotin, also known as vitamin B7, is a water-soluble vitamin that plays a crucial role in treatment of rare metabolic conditions like biotinidase deficiencies and propionic acidemia. In addition, the popularity of biotin supplementation for promoting hair, skin, and nail health has significantly increased recently. On the other hand, there exist several types of immunoassays for TFTs, which rely on the interaction between biotin and streptavidin. The high affinity between biotin and streptavidin can lead to the formation of biotin-streptavidin complexes, causing falsely elevated fT3 and fT4 levels and falsely low TSH level in subjects using biotin treatment.[50,51] When a child presents with elevated fT4-T3 levels and low TSH levels without symptoms of hyperthyroidism, administration of biotin should be investigated. It is recommended to repeat the measurement after discontinuing biotin use for 2–3 days. Alternatively, if discontinuation is not possible, it is advised to repeat the TFT using an assay that does not rely on biotin as a marker.[50]

**8. Familial Dysalbuminemic Hyperthyroxinemia**

Familial dysalbuminemic hyperthyroxinemia (FDH) is an autosomal dominant familial condition that was first documented in 1979.[52,53] It arises from an abnormal albumin molecule that exhibits an increased affinity for serum T4, despite normal quantitative levels of serum albumin. FDH does

not cause thyroid dysfunction but, depending on the assay used, it can affect serum TH levels. For instance, serum levels of fT4 and fT3 may be falsely elevated while serum TSH levels remain normal, resembling the syndrome of inappropriate secretion of TSH. Since individuals with FDH are clinically euthyroid and asymptomatic, treatment is unnecessary.[5,54]

**9. Resistance to Thyroid Hormone β (RTHβ)**

RTHβ is a rare disorder characterized by elevated levels of circulating free THs, inappropriately normal or rarely mildly elevated TSH secretion, and impaired peripheral tissue responses to the action of iodothyronines. In families, RTHβ typically follows an autosomal dominant inheritance pattern (80%), but it can also occur sporadically in individuals without a family history of RTHβ (20%).[11] Currently, over 3000 cases from approximately 1200 different families have been reported worldwide, with an equal frequency observed in both sexes and an estimated occurrence rate of 1 in 40,000 live births.[11,55]

The hallmark of RTHβ is the impaired response to TH mediated by the defective β receptor. This leads to resistance to TH action within the HPT axis, causing the persistent and nonsuppressed synthesis of TSH despite elevated levels of circulating TH. Many patients with RTHβ are asymptomatic and are incidentally diagnosed during thyroid function testing conducted for reasons unrelated to thyroid dysfunction However, the elevated TH levels may result in various degrees of hyperthyroidism in tissues expressing TRα.[35,56]

**Normal Free T4 with Elevated TSH**

**1. Subclinical Hypothyroidism**

Subclinical hypothyroidism (SH) is a biochemical definition in which the serum concentration of TSH exceeds the upper limit of the statistically defined reference range, while the serum concentrations of fT4 and fT3 remain within their reference ranges in at least two independent measurements which should be performed 4-12 weeks apart.[28,57,58] The upper limit of TSH for the definition of subclinical hypothyroidism is not clear. TSH levels between the upper limit of the reference range and 9.9 mU/L are classifed as mild or grade 1 SH while levels are equal or above 10 mU/L indicate severe or grade 2 SH.[57]

The prevalence of SH in adolescents is estimated to be around 2%. The majority of individuals with this condition are asymptomatic and do not exhibit any symptoms. In the pediatric population, SH is generally considered a benign and self-resolving condition with a low risk of progressing to overt hypothyroidism depending on the underlying etiology.[59] Risk factors for the progression to overt hypothyroidism include the presence of goiter, being female, experiencing symptoms or signs suggestive of hypothyroidism, and having strongly positive TPO antibodies. Limited data suggest that subclinical hypothyroidism itself does not appear to have any adverse effects on intellectual development, skeletal growth and maturation, or puberty.[60,61] Of note, biochemical evaluation of obese children reveals a high prevalence of elevated TSH levels (up to 7-9 mIU/L) with normal fT4 and fT3 levels. This condition may affect up to 20% of obese children, and studies have demonstrated that TSH levels tend to normalize with weight loss, indicating that thyroid dysfunction is likely a consequence of obesity rather than its primary cause.[5]

**2. Macro-TSH**

Macro-TSH is a distinct condition characterized by the presence of high-molecular-weight complexes of TSH in the bloodstream. These complexes, primarily bound to immunoglobulin G, exhibit low bioactivity and accumulate due to impaired clearance mechanisms. Macro-TSH can be falsely detected as hyperthyrotropinemia using standard immunoassays. The biochemical profile of individuals with macro-TSH resembles that of SH, with elevated serum TSH levels and normal fT4 levels. Therefore, interference should be suspected in a patient with isolated TSH elevation with THs in the upper half of the normal range, and without signs or symptoms of thyroid dysfunction.[50]

The polyethylene glycol (PEG) precipitation procedure, which is commonly used for screening macro-prolactinoma in hyperprolactinemic patients, has also been modified for the detection of macro-TSH. While the PEG precipitation procedure is practical and can be used as an initial screening test for the detection of macro-TSH, it is important to be aware that an increase in globulin concentration can lead to an elevated amount of precipitated TSH, potentially causing misclassification. As a result, gel filtration chromatography (GFC) is widely regarded as the preferred method for the precise identification of macro-TSH. In situations where PEG treatment results in a low recovery, confirmation through GFC is crucial.[50,62]

**Author contribution**

Concept: GAK, KD; Design: GAK, KD; Data Collection or Processing: GAK, KD; Analysis or Interpretation: GAK, KD; Literature Search: GAK, KD; Writing: GAK, KD. All authors reviewed the results and approved the final version of the article.

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Original Article

# Internet addiction and anxiety in asthmatic children after the first year of the COVID-19 pandemic*

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## ABSTRACT

**Objective:** Studies have revealed that people with asthma have a higher risk of anxiety during the COVID-19 pandemic. The relationship between internet addiction and anxiety has long been known, but to our knowledge, no studies have combined anxiety in asthmatic children and adolescents with internet use. This study investigated the relationship between anxiety levels and internet use in asthmatic children and adolescents during the late stage of the COVID-19 pandemic.

**Method:** A multicenter survey was conducted in February-March 2021, enrolling 78 asthmatic patients and 44 healthy controls. Anxiety was assessed with the State-Trait Anxiety Inventory for Children (STAI-C) for children aged 9-12 and with the State-Trait Anxiety Inventory (STAI) for adolescents aged 13-18. Internet use was assessed with the Internet Addiction Scale for Adolescents (IASA).

**Results:** Anxiety scores did not differ between patients and controls. The average time spent on the internet increased markedly (over three-fold) during the pandemic period compared to the pre-pandemic period (from 2.1±1.5 [0-6] hours per day to 6.9±3.5 [0-18] hours per day ($p<0.001$ in all participants). There was no difference in the IASA scores between the patients and controls. There was a correlation between the IASA and STAI state and trait (STAI [S] and STAI [T]) scores in the 13-18 year group ($r=0.28$, $p=0.03$, and $r=0.34$ $p=0.01$, respectively).

**Conclusion:** Problematic internet use has more impact on anxiety in adolescents than asthma during the late stage of the COVID-19 pandemic. We suggest that internet addiction should be kept in mind when evaluating anxiety in asthmatic adolescents during their follow-up.

**Keywords:** Anxiety, asthma, children, COVID-19 pandemic, internet addiction

## INTRODUCTION

As of April 2022, SARS-CoV-2 (COVID-19) had been reported to have caused 504,600,544 infections and 6,198,747 deaths worldwide[1] and to have severely affected both psychological and physical health. A global systematic review of psychological outcomes conducted among the public during the COVID-19 pandemic found relatively high rates of anxiety (6.33-50.9%), depression (14.6-48.3%), posttraumatic stress disorder (7-53.8%), psychological distress (34.43-38%), and stress (8.1-81.9%).[2]

Children have constituted only 1-5% of diagnosed COVID-19 cases so far; symptoms have been milder than adults, and deaths

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have been extremely rare.[3] At the beginning of the pandemic, some health authorities suggested that asthma and allergic diseases might be risk factors for COVID-19. It later became clear that only uncontrolled asthma is a risk factor for severe COVID-19 and that patients with common allergic diseases do not develop distinct symptoms or severe outcomes.[4,5] Nevertheless, this potential relationship still had a potentially detrimental impact on patients' perceptions of their COVID-19 risk and mental health status.

Various interactions between allergy-related inflammatory and psychiatric disorders, such as depression, anxiety, and affective disorders, have been documented.[6-8] As allergic diseases themselves are associated with a negative effect on anxiety and depression, the COVID-19 pandemic could have resulted in an additional increase in the anxiety and depression levels of these patients. Many studies have dealt with the psychological impacts of COVID-19 on people with allergic diseases, especially those with asthma in specific age groups.[9-15] A recently published comprehensive review revealed that people with asthma, allergic rhinitis, and other chronic respiratory diseases are at higher risk for negative psychological outcomes, with risk factors including asthma severity, female sex, and previous history of anxiety and depression, likely owing to the perceived risk of severe disease from COVID-19.[16]

On the other hand, previous studies revealed the association between pathological internet use and psychological problems in adolescents, such as depression[17,18] and anxiety.[19,20] Although there have been many studies on the psychological impact of COVID-19 on asthmatic patients, to our knowledge, no previous study has investigated both anxiety and Internet use in asthmatic children and adolescents.

In this study, we aimed to evaluate state and trait anxiety levels in asthmatic children and adolescents during the late stage of the COVID-19 pandemic and to evaluate their relationship with internet use. We also aimed to compare the results with those of age-matched healthy children.

## MATERIALS AND METHODS

### Study design and population

A multicenter survey was conducted at three pediatric allergy and immunology departments located in different cities of Türkiye: 1) Trakya University Medical Faculty/Edirne, 2) Kanuni Sultan Süleyman Training and Research Hospital/İstanbul and 3) Necip Fazıl City Hospital/Kahramanmaraş. The study was conducted between February and March 2021. The patients aged 9-18 years who had been followed up for asthma for at least one year at each study center were enrolled in the study.

The patients had been diagnosed with asthma according to the clinical diagnostic criteria of the Global Initiative for Asthma (GINA)[21], based on a history of variable respiratory symptoms, such as wheezing, shortness of breath, chest tightness, and cough, as well as evidence of variable expiratory airflow limitation using spirometry. Age- and sex-matched healthy children were enrolled as a control group. Children in the control group were recruited through snowball sampling from friends and relatives of the patients because healthy children did not go to hospitals during the study period, except in emergency situations, because of the risk of COVID-19 transmission. Except for the items regarding asthma, the survey questions were almost identical for the control group. Written informed consent was obtained from all participants before being included in the study.

### Data collection instruments

Data were collected from respondents in three forms: an ad hoc, study-related questionnaire and two (types of) standardized and validated self-report questionnaires, one on anxiety (with different versions) and the other on internet use.

Study-related questionnaire: The questionnaire was designed by the authors and contained questions related to demographic data, type of education received during the pandemic, and a visual analog score on a scale of 1-10 to assess the fear of infection with COVID-19 for all respondents. It also included questions about treatment adherence, follow-up, and management/course of the disease for those diagnosed with asthma.

Anxiety questionnaire: The State-Trait Anxiety Inventory was employed to assess state (STAI [S]) and trait (STAI [T]) anxiety in patients and controls aged 13-18 years. For the younger age group (9-12 years), the State-Trait Anxiety Inventory for Children was used for state (STAI-C [S]) and trait (STAI-C [T]) anxiety, respectively.

The STAI-C contains two separate scales, one to measure state anxiety and the other to measure trait anxiety. The former consists of 20 items asking children how they feel at the present time, the latter of 20 items asking children how they feel in general.

This measures relatively stable individual differences in anxiety trends. Items are scored on a three-point Likert scale ("hardly ever," "sometimes," and "often"). Each scale yields a score between 20 and 60, with higher scores indicating higher levels of anxiety. A validation and reliability study of the Turkish version made by Özusta yielded 0.82 and 0.81 for STAI-C (S) and (T), respectively.[22]

The STAI (here applied to the older group) is similar. The 20 state questions ask how participants feel "right now" using items that measure subjective anxiety, tension, nervousness, anxiety, and activation/arousal to evaluate the present intensity of current emotions, here on a four-point Likert scale ("not at all," "somewhat, "moderately so," and "very much so"). The 20 trait questions assess relatively stable aspects of "anxiety tendency" in situations of general calmness, trust, and security to evaluate the "in general" frequency of emotions, again on a four-point Likert scale ("almost never," "sometimes," "often," and "almost always"). Both scales yield a score of between 20 and 80, with higher scores indicating higher anxiety. A validation and reliability study of the Turkish version made by Öner and Le Compte found the internal reliability of the STAI (S) and STAI (T) to be 0.94-0.96 and 0.83-0.87, respectively.[23]

Internet use questionnaire: Internet use was assessed with the Internet Addiction Scale for Adolescents (IASA). Developed by Taş[24], this scale comprises nine items and one factor (it has no reverse-coded items). The responses of the scale evaluate the "general" frequency of emotions related to internet use, with a five-point Likert scale ("never," "rarely," "sometimes," "often" and "always"). Each scale yields a score of 9-45, with higher scores indicating higher levels of internet addiction. The correlation coefficient of the test-retest performed at a one-month interval is 0.72; Cronbach's alpha internal consistency coefficient is 0.81.

All forms of the questionnaires were distributed as hard copies by the authors at each study center during regular visits (for the patients) and by e-mail (to the controls). In total, they took approximately 25-30 minutes to complete.

### Statistical analysis

We performed statistical analysis using the IBM SPSS Statistics for Windows, V.25.0 (IBM, Armonk, New York, USA) software. Numerical variables were presented as mean ± standard deviation, while the median (Inter Quartile Range) and categorical variables were presented as numbers and percentages. The normality distribution of numerical variables was evaluated using the one-sample Shapiro-Wilk test. Categorical data of the patient and control groups were compared using the chi-square test ($\chi 2$).

The Mann-Whitney U test was used to compare anxiety and internet addiction scores between the groups. The Wilcoxon test was used for the comparison of pre-and post-pandemic values of disease control parameters in asthmatic patients. The Spearman correlation analysis was used to investigate the associations between anxiety and internet addiction scores. Multivariate logistic regression analysis was used to analyze whether the anxiety scores and internet addiction scale scores between the two groups were affected by variables found to differ between the two groups. All analyses were two-tailed, and $p<0.05$ was considered statistically significant.

## RESULTS

### Demographic characteristics and ad hoc survey

A total of 122 participants from three pediatric allergy and immunology departments were included in the study. There were 78 asthmatic patients and 44 sex- and age-matched healthy controls. The distribution of the respondents among the centers was 44.8%, 32%, and 23.2% from, respectively, the Trakya University School of Medicine, Kanuni Sultan Süleyman Training and Research Hospital, and the Necip Fazıl City Hospital.

The monthly income and education level of mothers and fathers were higher in the control group, whereas the number of people living at home was higher in the patient group. The demographic characteristics of the patients and controls are shown in Table 1.

Most of the respondents thought that they had adequate information about COVID-19 virus transmission, symptoms, and protective measures (95, 94.2, and 96.7%, respectively). All respondents were following distance education at home during the study because schools had been closed by the government.

The median follow-up time of the patients was 22.5 months. Most were using inhaled corticosteroids as maintenance therapy. There was a significant difference in the numbers of emergency service admissions and hospitalizations due to asthma exacerbation between the year before the pandemic and since the beginning of the pandemic. Only nine (11.5%) patients

| Table 1. Demographic characteristics of respondents | | | |
|---|---|---|---|
| | **Patients (n=78)** | **Controls (n=44)** | **p*** |
| Age, years median (IQR) | 11.5 (10-15) | 13 (10-14) | 0.89 |
| Gender (male) n (%) | 48 (61.5) | 26 (59) | 0.79 |
| Education level of mothers n (%) | | | |
| Primary, middle, and high school | 72 (92.3) | 25 (56.8) | p=0.000002 |
| University | 6 (7.7) | 19 (43.2) | |
| Education level of fathers n (%) | | | |
| Elementary, middle and high school | 67 (85.9) | 22 (50) | p=0.000009 |
| University | 11 (14.1) | 22 (50) | |
| Monthly income n (%) | | | |
| < 5000 TL | 59 (75.6) | 22 (50) | 0.004 |
| > 5000 TL | 19 (24.4) | 22 (50) | |
| The number of people living in the house: median (IQR) | 4.00 (5-4) | 4.00 (4-3) | p=0.0003 |
| Existence of any person in the family with increased risk of severe Covid-19 risk | 27 (34.6) | 13 (29.5) | 0.56 |
| Existence of any person in the family diagnosed with Covid-19 infection during the pandemic | 30 (38.4) | 12 (27.2) | 0.21 |
| Any isolation occurring in the family due to Covid-19 infection (Yes) | 29 (37.1) | 12 (27.2) | 0.26 |
| Average time to reach the hospital in case of an emergency | | | |
| < 30 minutes | 63 (80.8) | 38 (86.4) | 0.43 |
| > 30 minutes | 15 (19.2) | 6 (13.6) | |
| Existence of death due to Covid-19 in the family | 3 (3.8) | 1 (2.2) | 1 |
| IQR: Inter Quartile Range, *Mann-Whitney U test, Chi-Square test, Fisher exact test | | | |

had reported difficulties in securing their maintenance therapy during the pandemic. Thirty-three (42.3%) had experienced problems in contacting their doctor during the pandemic and 32 (41.0%) had avoided admission to Emergency Services (ES) for the fear of being infected with COVID-19 (Table 2).

**Internet use**

There was no statistical difference in the IASA scores between the patients and controls (Table 3). Asked about their average time spent on the internet before and during the pandemic, 90.1% of respondents reported an increase. A mean of 2.1±1.5 (0-6) hours was reported as spent on the internet in the pre-pandemic period and 6.9±3.5 (0-18) hours during the pandemic (p<0.001). There was no statistical difference between the patient and control groups (2.2±1.7 [0-6]) pre-pandemic and 6.7±3.7 [0-18] during the pandemic vs. 1.9±1.1 [0-5] pre-pandemic and 7.2±3.0 [1-14] during the pandemic; p=0.87 and 0.44, respectively).

**State/trait anxiety and relationship with internet addiction**

There were no significant differences between patients and controls when comparing the state and trait anxiety scores according to the age groups. We hypothesized that this might be related to the demographic characteristics that were found to be significantly different between the two groups. We created a model in multivariate logistic regression analysis to analyze whether the anxiety scores and internet addiction scale scores between the two groups were affected by these variables, which we found to be different between the two groups. We included the education level of mothers, the education level of fathers, monthly income, and the number of people living in the house in this model. We then performed a multivariate logistic regression analysis by putting all the anxiety scores and internet scores into this model one by one. As a result of this analysis, we again did not find a significant difference between the two groups (Table 3).

**Table 2. Treatment properties and clinical courses of the asthmatic patients (n=78)**

| | n (%) | In the last year before the pandemic, mean±SD | Since the beginning of the pandemic, mean±SD | p* |
|---|---|---|---|---|
| Use of any maintenance therapy | | | | |
| ICS | 63 (80.7) | | | |
| AIT | 16 (20.5) | | | |
| Any problem experienced in the providing of the maintenance therapy during Covid-19 pandemic | 9 (11.5) | | | |
| The number of days/week requiring bronchodilator therapy* | | 1.1±1.98 | 0.5±1.48 | p=0.00009 |
| The number of days/week missing maintenance therapy* | | 0.45±0.95 | 0.38±1.09 | 0.46 |
| The number ES admissions due to asth-ma exacerbation* | | 0.98±2.72 | 0.46±1.08 | 0.004 |
| The number hospitalization due to asth-ma exacerbation* | | 0.22±0.92 | 0.01±0.11 | 0.04 |
| Any problems contacting a doctor dur-ing the Covid-19 pandemic | 33 (42.3) | | | |
| Avoidance of admission to ES due to fear of being infected with Covid-19 | 32 (41.0) | | | |

*Wilcoxon test, ICS: Inhaler Cortico Steroid, AIT: Allergen Immunotherapy, ES: Emergency Service

**Table 3. Anxiety and internet addiction scale scores of the patient and control groups and multivariate logistic regression analysis to model the possible variables related to the anxiety scores and the internet addiction scale scores**

| Age group | Scores | Patients (n=78) Median (IQR) | Controls (n=44) Median (IQR) | Crude p* | Adjusted p ** | Adjusted OR (95% CI)** |
|---|---|---|---|---|---|---|
| 9-12 | STAI-C (S) | 45.0 (48.0-43.0) | 49.0 (50.0-41.5) | 0.28 | 0.881 | 0.99 (0.87-1.13) |
| 9-12 | STAI-C (T) | 35.0 (40.0-31.0) | 38.5 (44.0-33.5) | 0.11 | 0.175 | 0.94 (0.85-1.03) |
| 13-18 | STAI-(S) | 36.0 (41.0-29.0) | 40.0 (44.2-31.0) | 0.20 | 0.392 | 0.97 (0.89-1.05) |
| 13-18 | STAI-(T) | 35.0 (45.0-31.0) | 39.0 (45.7-32.0) | 0.33 | 0.184 | 0.95 (0.89-1.02) |
| 10-18 | IASA | 16.0 (21.0-13.0) | 17.0 (22.0-14.0) | 0.17 | 0.172 | 0.95 (0.89-1.02) |

IQR: Inter Quartile Range, CI: confidence interval; OR: odds ratio;
STAI-C (S): State-Trait Anxiety Inventory for Children, State, STAI-C (T): State-Trait Anxiety Inventory for Children, Trait, STAI-(S): State-Trait Anxiety Inventory, State, STAI-(T): State-Trait Anxiety Inventory, Trait, IASA: Internet Addiction Scale for Adolescents
*Mann-Whitney U test **Adjusted for education level of mothers, education level of fathers, monthly income, the number of people living in the house

**Table 4. Correlation analysis between anxiety scores and the internet addiction scale score**

| | STAI-C (S) | STAI-C (T) | STAI-(S) | STAI-(T) |
|---|---|---|---|---|
| IASA | r: 0.09<br>p: 0.47 | r: 0.17<br>p: 0.17 | r: 0.28*<br>p: 0.03 | r: 0.34*<br>p: 0.01 |

r: correlation coefficient,
STAI-C (S): State-Trait Anxiety Inventory for Children, State, STAI-C (T): State-Trait Anxiety Inventory for Children, Trait, STAI-(S): State-Trait Anxiety Inventory, State STAI-(T): State-Trait Anxiety Inventory, IASA: Internet Addiction Scale for Adolescents

Correlation analysis for anxiety and internet addiction in the 13-18 age group revealed a correlation between the IASA and the STAI (S) and (T) scores (r=0.28, p=0.03, and r=0.34, p=0.01, respectively) (Table 4).

**Fear of COVID-19 Infection**

There was no difference between the patients and controls in terms of their subjective visual analog scores for fear of COVID-19 infection (median [IQR] 5.5 (7.2-4.0) vs. 6 [7.0-4.0], p=0.98).

## DISCUSSION

This case-control study focused on the assessment of asthmatic children and adolescents in the context of state-trait anxiety during the late stage of the COVID-19 pandemic. To the best of our knowledge, it is the first study to combine this with an evaluation of the impact of internet use on anxiety.

We found no difference between the anxiety scores of asthmatic patients and their healthy peers, but there was a correlation between state-trait anxiety scores and internet addiction scale scores in the 13-18 age group.

It is well known that there is a relationship between psychiatric comorbidities and symptom control, medication adherence, and exacerbations in asthma.[21] As allergic diseases themselves are associated with a negative effect on anxiety and depression, the COVID-19 pandemic could result in an additional increase in anxiety and depression levels in these patients.

Studies conducted in the immediate aftermath of the lockdown due to the COVID-19 pandemic showed that patients with asthma, allergic rhinitis, and other chronic respiratory diseases were at higher risk for negative psychological outcomes.[11-13,16] Among these studies, two conducted in asthmatic adults are noteworthy here because they included data comparing anxiety and depression scores between the pre-pandemic period and shortly after the lockdown. Both showed asthma to be associated with a decline in mental health status during lockdown.[11,12] These results were not surprising. The impact of the pandemic on mental health was very strong even in the general population[2], and the link between asthma and COVID-19 was still being debated at the time they were performed, when it was unclear whether asthma might be considered a risk factor for severe COVID-19 infection. In addition, lockdowns may result in social isolation, which is known to have a negative impact on anxiety and depression levels.[25]

It is likely that the psychological rather than physical effects of the pandemic and/or lockdown had a greater impact on the mental health of people with asthma in the early period of the pandemic. Indeed, a later study from Italy, after the lockdown, by Di Riso et al.[10] performed as an online survey, showed that asthmatic children presented no difference in psychological functioning evaluated as psychological adjustment (Strengths and Difficulties Questionnaire, SDQ) and separation anxiety (Separation Anxiety Factor of the Spence Children Anxiety Scale, SCAS-SAD). Our study was also performed during the later period of the pandemic, and our results are compatible with this study, despite the differences in methodology. The period of the study may be more important than whether participants have asthma or not. During the pandemic, it became clear that only uncontrolled asthma is a risk factor for severe COVID-19 and that patients with common allergic diseases do not develop distinct symptoms or severe outcomes.[4,5] Moreover, social isolation measures had been reduced by the later stages of the pandemic, so the anxiety levels of these patients might be expected to have diminished by then.

In our study, most asthmatics were using inhaled corticosteroids as maintenance therapy. Although 42.3% experienced a problem in contacting their doctor, they never considered stopping their current medication. They also reported an improved clinical disease course when comparing the year before the pandemic with the period since its onset. However, this may be mitigated, since, in Turkey, the supply of maintenance drugs used in the treatment of chronic diseases was allowed by the government without a prescription during the pandemic, and only 11.5% of the patients reported that they had difficulties in the provision of their maintenance therapy. Previous studies have similarly found increased adherence to asthma medication and improved asthma control during the pandemic[26,27], which may be another important factor that played a role in controlling patients' anxiety levels.

In our study, patients' subjective visual analog scores for fear of being infected with COVID-19 were not higher than those of the healthy controls. However, 41% of the asthmatic patients had avoided admission to ES since the beginning of the pandemic due to the fear of infection. Compatible with our results, previous studies revealed that adult asthmatic patients were relatively afraid of acquiring the COVID-19 disease and likely to avoid using healthcare facilities as a result.[12,14] It was also reported that Italian asthmatic children were more concerned about contagion than non-asthmatics.[10] It is possible that improved adherence to asthma medication in all countries might have been related to the fear of being infected with COVID-19 and avoidance of healthcare facilities.

We found a sharp increase in the time spent on the internet during the pandemic among all respondents. There was no statistical difference between the patients and controls in terms of the time that they spent on the internet and their IASA scores. Correlation analysis between anxiety scores and internet addiction scale scores revealed a correlation between the IASA and state and trait STAI scores in the 13-18 age group. Ha et al.[17] reported a significant association between internet addiction and depressive symptoms in 452 Korean adolescents. In another cross-sectional study, conducted among 440 upper secondary schools/colleges students, the prevalence of internet addiction was found to be 80.7%, and there was a significant association between internet addiction and stress, depression, and anxiety.[20]

We think that the relationship between IASA scores and anxiety scores was the most important result of our study, because the STAI scores suggested a moderate level of anxiety in patients and even in controls. This result did not differ even after multivariate logistic regression analysis, performed to eliminate the effect of potential confounding factors, such as education or the socio-economic status of the families.

Thus, excessive internet use might have had a greater impact on anxiety than the presence of allergic diseases during the late period of the COVID-19 pandemic.

Our study has three main strengths. One is that the asthma was not only self-reported but diagnosed by pediatric allergists in each study center. This means our study population was well-characterized. Another is that this is the first study to simultaneously evaluate the impact of internet use on anxiety scores in patients with allergic diseases during the COVID-19 pandemic. The third strength is that the analyses of anxiety and internet addiction were performed using standardized and validated scales.

There are some limitations in this study. First, pre-pandemic data on anxiety were not available, and therefore we could not make comparisons to assess the independent impact of the COVID-19 pandemic on our results. Second, we did not evaluate the main purpose of internet use; thus, we have no data on the ratio of educational time to time spent on other activities, such as playing games or engaging in social media.

## CONCLUSION

This study has revealed no difference in anxiety scores between asthmatic patients and their healthy peers during the late stage of the COVID-19 pandemic. However, there was a correlation between state and trait STAI scores and internet addiction scale scores in the older (13-18) age group. Considering the well-known relations in asthma between psychiatric comorbidities and symptom control and between medication adherence and exacerbation, it is important to be aware that internet addiction may be a relevant anxiety-related factor. Therefore, we suggest that the follow-up of these patients should include an evaluation for excessive internet use and referral to a psychiatrist when necessary, especially during adolescence.

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**Ethical approval**

This study has been approved by the Trakya University Faculty of Medicine Scientific Research Ethics Committee (approval date 18.01.2021, number 2020/366). Written informed consent was obtained from the participants.

**Author contribution**

Concept: PGÖ, VÇ, BB, ÖTU, SK, MY; Design: PGÖ, MY; Data Collection or Processing: PGÖ, VÇ, BB, ÖTU, SK; Analysis or Interpretation: PGÖ, VÇ; Literature Search: PGÖ; Writing: PGÖ, VÇ, BB, ÖTU, SK, MY. All authors reviewed the results and approved the final version of the article.

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**Conflict of interest**

The authors declare that there is no conflict of interest.

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Original Article

# Evaluation of renal function and ambulatory blood pressure monitoring in children and adolescents: The role of birthweight

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## ABSTRACT

**Objective:** A marked relationship is known between low birth weight and reduced nephron number. In this study, it was aimed to investigate the effects of low birth weight on renal function and blood pressure in healthy children and adolescents.

**Methods:** This study was carried out on 33 children (7 to 18 years) who were born with a birth weight under 2500 g. The control group was composed of 30 children born at term with a birth weight appropriate for gestational age. Urine microalbumin, N-Acetyl-β-D Glucosaminidase, sodium levels and blood urea nitrogen, creatinine, and cystatin-C levels were investigated in patients and the control group. The sizes of kidneys in both groups were examined by ultrasonography. Blood pressure was monitored for 24 hours as ambulatory blood pressure.

**Results:** The study group had higher levels of blood cystatin-C, urinary sodium, and N-Acetyl-βD-Glucosaminidase than the control group. Kidney volumes were smaller in the study group than in the controls.

**Conclusion:** In our study, we observed that some glomerular and tubular functions were affected in children with low birth weight and in children born preterm. These effects were not observed in children with mature small for gestational age. Considering that nephron formation is completed at the 37th week, gestational age (prematurity) was thought to affect glomerular maturation more than intrauterine growth retardation. Our findings did not demonstrate hypertension in children born with low birth weight in childhood. We suggest that low birth weight children should be followed carefully for renal functions and blood pressure.

**Keywords:** Children, cystatin-C, low birth weight, renal function tests

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## INTRODUCTION

The fetal origins hypothesis proposes that an early life environment has significant impacts on health in later life.[1] Especially, low birth weight (LBW) has been shown to have a relationship with renal diseases and hypertension at different ages in later life.

A marked relationship has been reported between LBW and reduced nephron numbers. Brenner et al.[2] showed that the filtration area in kidneys with low nephron numbers is reduced compared to healthy individuals with normal nephron numbers. This was confirmed by human postmortem and animal studies, in which LBW was associated with fewer nephrons and thereby a reduced kidney weight/volume.[3,4] It is important to identify early signs of kidney disease before the damage is done. Laboratory tests showing early structural and functional changes should be performed at regular intervals to detect patients at elevated risk of developing kidney damage. A variety of tests are used clinically to measure renal function. Glomerular filtration rate (GFR) is the finest measurement of kidney function in children and has a major role in the diagnosis of acute and chronic kidney damage. Creatinine clearance-based evaluation of GFR is frequently used in pediatrics. The inaccuracy of creatinine-based estimates of GFR, particularly in children with reduced muscle mass, is well known.[5] Recently, studies have declaimed the use of serum cystatin C as a new marker for the evaluation of early renal impairment. Another method for evaluating glomerular kidney function is the assessment of albuminuria and proteinuria.[6] N-acetyl-beta-Dglucosaminidase (NAG), which cannot be filtered by the glomerulus, is a well-known early marker of proximal tubular injury.[7]

Birth weight and hypertension are known to be negatively associated.[1] Ambulatory blood pressure monitoring (ABPM) for the evaluation of pediatric hypertension has been used in children and adolescents over the past 25-30 years. ABPM, which can more precisely characterize changes in BP throughout daily activities, has been found to be superior to office BPM (OBPM) in predicting cardiovascular morbidity and mortality.[8]

Estimation of renal size by ultrasonography (US) may be used as a surrogate measure for nephron number and as an indirect indicator of renal growth under different clinical conditions.[9]

The aim of the study was to examine the effects of LBW on kidney function, kidney dimensions, and blood pressure levels in healthy children and adolescents.

## MATERIAL AND METHODS

### Patients

The study group consisted of children who had been born with LBW and had no history of diseases or drug treatment during the study period. LBW was defined as birth weight under 2500 grams. LBW is further classified as very low birth weight (VLBW<1500 g) and extremely low birth weight (ELBW<1000 g).[10] Prematurity was described as babies born before 37 completed weeks of gestation. Sub-classes of preterm birth are extremely preterm (less than 28 weeks), very preterm (28 to 32 weeks), and late preterm (32 to 37 weeks).[11] Children were classified as small for gestational age (SGA) and appropriate for gestational age (AGA) based on Lubchenco's charts.[12]

The control group consisted of children who were all born at term with a birth weight appropriate for their gestational age. Both groups were selected from the pediatric outpatient clinics and were seen because of minor illnesses.

Birth weight data, personal (including information about birth weight, neonatal intensive care hospitalizations, and risk factors for hypertension or impaired kidney functions during the neonatal period) and family medical histories were obtained by a questionary with parents. Exclusion criteria were the presence of chronic illness, renal disease, drug use, or any of the above-mentioned risk factors that could affect renal function. Anthropometric measurements were made for each child. BMI was calculated as weight (kg)/height ($m^2$).

### Biochemical analyses

Blood samples were measured by a routine biochemistry analyzer to determine serum urea and creatinine levels. Serum cystatin C levels were measured with an enzyme-linked immunosorbent assay (ELISA) method, and the results were recorded as ng/ml. GFR was calculated from the serum creatinine, the child's height, and a proportionality constant using the original Schwartz method.[13]

The 24-hour urine protein, microalbumin, and Na levels were measured by a routine biochemistry analyzer. The urinary NAG levels were measured by a spectrophotometric method with a colorimetric kit (Diazyme Laboratories, 12889 Gregg Court Poway, CA 92064, USA). NAG levels in the samples were calculated using the following equation and given as IU/L. Sample Absorbance - blank solution absorbance/Standard Absorbance - blank solution absorbance = IU/L.[14]

### Ultrasonographic assessment

Kidneys were measured by the same radiologist using the same ultrasound system. Kidney dimensions (length, thickness, width), anterior-posterior diameter (AP), and cortical thickness were measured. Kidney measurements were assessed with respect to the reference values defined by Rosenblum et al.[15] Kidney volume was calculated by the formula for an ellipsoid (length × thickness × width × 0.5233). The measurements were assessed with respect to the reference values defined by Oswald et al.[16]

### Ambulatory blood pressure monitoring

Ambulatory blood pressure monitoring (ABPM) was performed using the oscillometric Welch Allyn 24-hour ABP Monitor, version 12, combined with an appropriate-sized cuff placed on the non-dominant hand during a hospital stay. The ABPM records were analyzed for mean systolic (SBP) and diastolic (DBP) arterial blood pressure during sleep (nighttime) or when awake (daytime) over the 24-h period. The BP loads for systolic and diastolic pressure were also recorded. The results of ABPM were assessed using the method of Soergel et al.[17] Non-dipping was defined as a fall in average sleeping systolic or diastolic BP < 10% from baseline. Blood pressure loads were considered as the percentage of systolic and diastolic BP readings greater than the 95th percentile. Loads in excess of 25% were considered elevated. Loads in excess of 50% were considered severely elevated.

### Statistical analyses

All statistical analyses were performed using the SPSS version 14 software package. The normal distribution of numeric variables was tested with the Kolmogorov-Smirnov test. Independent sample t-test was used for the comparison of normally distributed numeric variables. Mann-Whitney U test was used for the comparison of non-normally distributed variables. Pearson's or Spearman's correlation tests were used to determine the correlations between various measurements. P values less than 0.05 were considered statistically significant.

## RESULTS

The study group was composed of 33 children: 20 girls and 13 boys with a mean age of 10.0±2.3 years. The mean birth weight of the study group was 2000.6±387.6 g (1100-2450 g); 81.8% of the children were LBW, and 18.2% of the children were VLBW. Twenty-three of the LBW neonates were preterm birth and ten were term birth. Ten of the LBW neonates were SGA. The control group was composed of 30 healthy children (15 girls, 15 boys)

**Table 1. Anthropometric parameters of the LBW and the control groups**

| | LBW group (n=33) | Control (n=30) | p |
|---|---|---|---|
| Gender (Girl/Boy) | 20/13 | 15/15 | 0.39 |
| Age, years | 10.0±2.3 | 11.1±2.8 | 0.1 |
| Birth weight (g) | 2000.60±387.65 | 3451.65±473.86 | 0.000* |
| Current Weight Percentile | | | |
| <3p | - | - | 1 |
| 3-97p | 30 (90.9%) | 27 (90%) | |
| >97p | 3 (9.1%) | 3 (10%) | |
| Current Height Percentile | | | |
| <3p | 2 (6.1%) | - | 0.49 |
| 3-97p | 31 (93.9%) | 30(100%) | |
| >97p | - | - | |
| Current BMI | 35.5 | 28.7 | 0.13 |
| Current BMI Percentile | | | |
| <3p | 2 (6.1%) | 1 (3,3%) | 0.96 |
| 3-85p | 26 (78.8%) | 24 (80%) | |
| 85-95p | 1 (3%) | 1 (3.3%) | |
| >95p | 4 (12.1%) | 4 (13.3%) | |

LBW: Low birth weight

| Table 2. Renal function of the LBW and control groups | | | |
|---|---|---|---|
| | **LBW group (n=33)** | **Control (n=30)** | **p** |
| Serum urea (mg/dl) | 24.66±5.72 | 21.46±4.64 | 0.018* |
| Serum creatinine (mg/dl) | 0.53±0.05 | 0.57±0.08 | 0.022* |
| Serum cystatin C (ng/ml) | 2450.03±344.00 | 2216.83±191.00 | 0.002 * |
| GFR (ml/min/1.73 $m^2$) | 143.00±13.79 | 145.00±13.74 | 0.426 |
| Urine Na (mEq/L) | 144.60±243.60 | 138.86±71.70 | 0.012* |
| Urine NAG (IU/L) | 0.44±0.04 | 0.41±0.03 | 0.014* |
| Urine microalbumin (µg) | 12.80±17.71 | 17.5±14.4 | 0.017* |
| | (median:8) | (median:12) | |
| Urine protein (mg/$m^2$/h) | 3.44±1.77 | 4.07±1.96 | 0.187 |

*Significant difference (P<0.05) compared to controls.
GFR: Glomerular filtration rate, NAG: N-acetyl-beta-D-glucosaminidase, Na: sodium, LBW: Low birth weight

with a mean age of 11.1±2.8 years. The mean birth weight of the control group was 3451.6±473.8g (2550-4300g). The study group consisted of 15 (45.5%) children admitted to the NICU during the neonatal period. Of these, 6 (18.2%) received mechanical ventilation, 2 (6.1%) had an umbilical vein catheterization, and 9 (27.3%) used drugs in that period. The control group consisted of 4 (13.3%) children admitted to the NICU during the neonatal period, none of whom needed invasive procedures or drug therapy. The age, gender, weight, height, and BMI percentiles of the patients were not statistically different between the LBW and control groups (Table 1). The renal functions of the LBW group and the control group are shown in Table 2. The GFR in the LBW group was not significantly different compared to the control group (Table 2). There was a significant correlation between GFR and current weight in the LBW group (r=0.486, p=0.004). The mean urea levels were significantly higher in the children-with-LBW group in comparison to the control group. The mean serum creatinine levels were significantly lower in the children-with-LBW group in comparison to the control group (t=-2.29, p=0.022). Serum creatinine levels were positively associated with the current weight of the children (r=0.471, p=0.006), but there was no significant correlation between serum creatinine levels and birth weight. The mean urea, serum creatinine levels, and GFR were similar between the children born preterm and term. Also, the mean serum creatinine levels and GFR were similar between the children born SGA and AGA. The mean serum urea levels were significantly higher in the SGA group than in the AGA group (Table 3).

The mean blood cystatin-C levels were found to be significantly higher in the children-with-LBW group compared to the control group (Table 2). The mean blood cystatin-C levels were also significantly higher in children born preterm compared to the children born term (p=0.002). Blood cystatin-C levels were similar in children born SGA and AGA (p=0.23). A negative relationship was found between blood cystatin-C levels and birth weight in the study group (Figure 1). No significant association was found between blood cystatin-C levels and current weight in either group.

Urine Na and NAG levels were significantly increased, and microalbumin levels were significantly decreased in the children-with-LBW group in comparison to the control group.

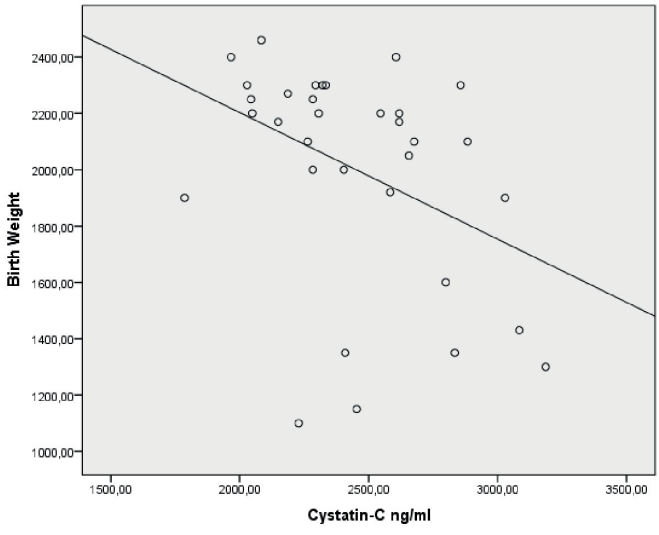


**Figure 1.** Correlation between blood cystatin C and birth weight

| Table 3. Renal functions of children according to their gestational week and birth weight classifications | | | |
|---|---|---|---|
| | **Children born as preterm (n=23)** | **Children born as term (n=40)** | **p** |
| Serum urea (mg/dl) | 23.5±1.2 | 22.9±0.79 | 0.66 |
| Serum creatinine (mg/dl) | 0.5±0.1 | 0.56±0.01 | 0.08 |
| Serum cystatin C (ng/ml) | 2530.3±0.7 | 2228.9±32.4 | **<0.0001** |
| GFR(ml/min/1.73 $m^2$) | 143.7±3.2 | 144.6±2 | 0.8 |
| Urine Na (mEq/L) | 172.8±60 | 124±11 | 0.34 |
| Urine NAG (IU/L) | 0.44±0.008 | 0.42±0.005 | **0.043** |
| Urine microalbumin (µg) | 13.5±4.2 | 16±2.1 | 0.4 |
| | **SGA (n=10)** | **AGA (n=53)** | |
| Serum urea (mg/dl) | 27.1±4.6 | 22.1±5.2 | 0.02 |
| Serum creatinine (mg/dl) | 0.52±0.1 | 0.54±0.1 | 0.26 |
| Serum cystatin C (ng/ml) | 2236.8±268.1 | 2363.0±308.8 | 0.23 |
| GFR(ml/min/1.73 $m^2$) | 141.3±7.6 | 143.8±14.7 | 0.23 |
| Urine Na (mEq/L) | 1.8±0.3 | 1.6±0.4 | 0.21 |
| Urine NAG (IU/L) | 0.42 | 0.42 | 0.31 |
| AGA: appropriate for gestasional age, SGA: small for gestasional age | | | |

| Table 4. ABPM parameters of the LBW and control group | | | |
|---|---|---|---|
| | **LBW group (n=33)** | **Control (n=30)** | **p** |
| **Mean blood pressure (mean±standart deviation)** | | | |
| Daytime systolic (mmHg) | 106.6±9.1 | 108.2±9.8 | 0.510 |
| Daytime diastolic (mmHg) | 60.6±5.5 | 61.8±7.0 | 0.469 |
| Nighttime systolic (mmHg) | 99.9±9.4 | 101.6±11.0 | 0.523 |
| Nighttime diastolic (mmHg) | 56.3±6.2 | 57.1±7.3 | 0.643 |
| **Blood Pressure loads (BPL) (median levels) (%)** | | | |
| Daytime systolic BPL | 6.0 | 4.0 | 0.35 |
| Daytime diastolic BPL | 2.0 | 0 | 0.65 |
| Nighttime systolic BPL | 0 | 0 | 0.75 |
| Nighttime diastolic BPL | 7.0 | 11.0 | 0.85 |
| ABPM: Ambulatory blood pressure monitoring, LBW: Low birth weight | | | |

Urine NAG levels were significantly increased in children born preterm compared to the term group (Table 3, p=0.043). Urine Na and NAG levels were similar between the children born SGA and AGA (Table 3).

A mean of three manual blood pressure measurements was normal in all children. According to the ABPM results, a small number of children in the study group (3.4% of them had daytime systolic blood pressure, 12.9% had nocturnal systolic and 6.5% had nocturnal diastolic blood pressure) had high blood pressure. However, the two groups (LBW and control) did not differ in terms of systolic and diastolic blood pressures and blood pressure loads (Table 4). The ratio of non-dipping was found to be 77.4% and 63% in the LBW children and the control groups respectively, but there was no significant difference between the groups. Additionally, mean BP levels and BP loads were similar in children born SGA and AGA.

**Table 5. Renal size in the LBW and the control group**

| | | LBW group (n=33) | Control (n=30) | p |
|---|---|---|---|---|
| Volume | Left ($mm^3$) | 89.50±25.10 | 104.43±32.69 | 0.047* |
| | Right ($mm^3$) | 89.69±28.70 | 102.86±30.60 | 0.833 |
| Lenght | Left (mm) | 92.81±7.80 | 97.41±11.40 | 0.078 |
| | Right (mm) | 90.72±8.50 | 93.93±10.70 | 0.194 |
| Depth | Left (mm) | 41.62±4.30 | 42.86±5.70 | 0.196 |
| | Right (mm) | 41.06±5.40 | 43.96±6.50 | 0.058 |
| Width | Left (mm) | 43.40±5.30 | 45.50±5.90 | 0.151 |
| | Right (mm) | 44.31±6.10 | 46.06±5.90 | 0.254 |
| Parenchym | Left (mm) | 14.28±2.50 | 14.91±2.20 | 0.314 |
| | Right (mm) | 13.81±2.20 | 13.93±2.10 | 0.868 |
| AP diameter | Left (mm) | 3.87±0.70 | 4.13±0.90 | 0.329 |
| | Right (mm) | 4.06±0.80 | 4.03±0.90 | 0.713 |

*Significant difference (P<0.05) compared to controls.
LBW: Low birth weight

The low-birth-weight group had smaller kidney size (width x length x depth) in comparison to the control group. However, no significant difference was found between the groups (Table 5). Left kidney volumes were smaller in the LBW group compared to controls, despite the fact that all kidneys were anatomically normal (p=0.04). Kidney volumes were positively associated with the current weight of the children, but there was no significant correlation between kidney volumes and birth weight. Renal sizes were not statistically significantly different between the groups compared with age-adjusted normal values.

## DISCUSSION

In 2017, the Low Birth Weight and Nephron Number Working Group issued a consensus document emphasizing the relationship between preterm birth, low birth weight, IUGR, and reduced nephron number.[18] LBW could be due to prematurity (AGA) or secondary to intrauterine growth restriction (IUGR-SGA). This study investigated the effects of LBW, preterm birth, and SGA on renal function and blood pressure. We found that LBW and preterm birth affected some glomerular and tubular functions in childhood.

In the fetus, GFR parallels the gestational age and body weight. GFR increases after birth and come to adult levels in humans by the age of two years.[19] Vanpee et al.[20] assessed kidney function in VLBW infants and the GFR remained lower at nine months of age compared to term infants. At eight years of age, the GFR was not different from that of healthy children. Another study showed that the mean GFR was the same in both the SGA and AGA groups.[21] Our results were also similar to these findings. The GFR values were normal in all groups, and we found no significant difference between children-with-LBW and control groups. The mean GFR was similar in both the SGA and AGA groups.

Serum creatinine level is often used to evaluate renal function. However, serum creatinine level is not only detected by its renal excretion but also by its production in muscular tissue, which is dependent on gender, weight, age, and protein intake. Two studies showed similar serum creatinine values in both the SGA and AGA groups, and there were no signs of tubular or glomerular damage in the SGA children.[22,23] On the contrary, Keijzer-Veen et al.[24] showed that subjects born SGA had lower GFR and higher serum creatinine concentration at the age of 19. In our study, we found increased levels of serum urea and decreased levels of serum creatinine in LBW children. Both serum urea and serum creatinine levels were in the normal range in all groups. These conflicting results suggest that serum urea and creatinine levels cannot be used as early markers of kidney damage in these children. Although there was no overall association between birth weight and serum creatinine levels, a significant positive correlation was found between current body weight and serum creatinine levels. The major reason for this variability is thought to be the fact that creatinine is a protein produced in muscle tissue.

Serum cystatin C level is another marker of GFR. In children, the cystatin C levels stabilize from the second year of life, and the reference range is similar to that of adults. Moreover, cystatin C production is not influenced by age, gender, muscle

mass, or protein intake.[25] Studies comparing serum cystatin C levels in LBW children and normal birth weight children are increasing. Kwinta et al.[26] showed that serum cystatin C levels were significantly increased in the ELBW group. Our study revealed that serum cystatin C levels were significantly higher in LBW children compared to the control group, and a negative relation was found between birth weight and serum cystatin C levels. While serum cystatin C levels were significantly higher in children born preterm compared to those born term, they were similar in children born SGA and AGA. High plasma levels of cystatin C, despite normal creatinine levels and normal GFR values, are thought that plasma levels of cystatin C may be used as a better marker of kidney damage in these children.

Microalbuminuria projects an increase in glomerular vascular permeability. Many studies have shown the prevalence of microalbuminuria to be 2.7%-12.5% in children born with LBW.[23,26-28] Some studies identified that there is increased microalbuminuria in young adults born with LBW.[24,29] In accordance with this finding, two other studies reported that urinary protein excretion was similar in children born SGA and AGA at term.[22,30] In our study, urinary microalbumin excretion was found to be reduced in children with LBW compared to the control group. Urinary protein excretion was similar in the children-with LBW and the control group. Urinary microalbumin and protein excretion were similar in children born SGA and AGA. The lack of association between birth weight and urinary microalbumin excretion suggests that renal impairment, which can be detected by urinary microalbumin excretion, had not begun in this age group yet.

Urinary NAG excretion is used as a predictor of tubular cell dysfunction and damage.[30] Monge et al.[29] detected higher NAG excretion in children born with LBW. Other studies showed that there was no evidence of glomerular and tubular injury in children with LBW.[22,30] Our study revealed that urinary NAG excretion was increased in children with LBW and born preterm in comparison to the control group. Urinary NAG excretion was similar in children born SGA and AGA. We found that urinary microalbumin excretion was decreased in children with LBW compared to the control group, although all values were within normal ranges in both groups. The increase in NAG excretion, although a normal microalbumin excretion, confirmed that the level of NAG excretion might be an early and more accurate test to evaluate an initial malfunction or injury of the proximal tubular epithelial cells in the early phase of renal disease. Significantly elevated urinary NAG excretion in the study group also indicated proximal tubular damage in the children with LBW and born preterm.

It has been shown that the activation of the urinary renin-angiotensin system decreases the urinary excretion of sodium in LBW children and is associated with hypertension.[26] In our study, contrary to expectations, urinary sodium excretion rates were higher in the children-with-LBW group in comparison to the control group. an increase in urinary Na excretion may be the result of tubular damage.

Many studies have shown that LBW is related to hypertension in childhood and adult life.[31-33] On the contrary, Bilge et al.[30] suggested that no difference was observed between SGA and AGA children based on clinic and ambulatory blood pressure measurements. Rakow et al.[22] showed that blood pressure did not differ between SGA and AGA children. In our study, the mean blood pressure level was similar in children with LBW, born preterm, SGA and the control group. Our findings did not show the effect of low birth weight, prematurity, and IUGR on blood pressure in early childhood.

Many studies have demonstrated that LBW is associated with decreased kidney size in infants, children, and adults.[27,34,35] On the other hand, some studies found no differences in mean percentiles for renal length and volume compared to healthy control children and infants born with LBW.[28,33] In our study, the LBW group had an insignificantly smaller kidney size compared to the control group. Kidney volumes in these children were also strongly correlated with their current body weights.

## CONCLUSION

As a result, in our study, we observed that some glomerular and tubular functions were affected in children with low birth weight and in children born preterm. These effects were not observed in children with mature SGA. Considering that nephron formation is completed at the 37th week, gestational age (prematurity) was thought to be more effective in completing maturation rather than intrauterine growth retardation. We suggest that low birth weight children should be followed for renal functions in childhood. More extensive studies of renal activity in children with low birth weight are needed in the future.

### Limitations

The weaknesses of the study are the small sample size, the improper distribution of the population size, and all the data about the neonatal period was obtained by a questionnaire with the parents.

### Ethical approval

The study protocol was approved by the Institutional Review Board of Adnan Menderes University Medical Faculty (Reference Number: 2010/031) and it was conducted in accordance with the World Medical Association's Declaration of Helsinki. Informed consent was obtained from both parents for each child.

### Author contribution

Concept: FS; Design: FS; Data Collection or Processing: NK, AÜ, ÇY; Analysis or Interpretation: MÖ; Literature Search: NK, İG; Writing: NK, İG. All authors reviewed the results and approved the final version of the article.

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### Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

# Determination of pediatric nurses' knowledge of and attitudes towards childhood autism and CT recommendations

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## ABSTRACT

**Objective:** The study aimed to determine the knowledge levels and attitudes of nurses working in pediatric clinics on childhood autism and which complementary therapies (CT) methods they recommend to support children with autism

**Methods:** The study was designed as a descriptive research and the data were collected online. This study was conducted with 135 pediatric nurses. Research data were collected through the Sociodemographic Information Form, the Societal Attitudes Toward Autism (SATA) Scale, and the Knowledge about Childhood Autism among Health Workers (KCAHW) Questionnaire.

**Results:** While the mean score for the SATA scale of the nurses participating in the study was 48.46±9.84, the mean score of the KCAHW questionnaire was 8.13±3.81. The mean scores for the subdimensions of the SATA scale was 7.93±2.49 at the lowest and 28.33±6.11 at the highest. In this study, nurses suggested six different CT practices in total, with exercise being the most frequently recommended one.

**Conclusion:** The level of knowledge on childhood autism among our participants was found to be above average. In addition, in this study, the knowledge level of pediatric nurses was related to their attitudes towards individuals with autism at a very high level. Therefore, it is recommended to prepare a guide on autism and CT suggested by the nurses. It is recommended to plan the necessary interventions to improve the knowledge and attitudes of pediatric nurses about autism and to prepare a guide about CT to be used by nurses.

**Keywords:** Attitude, autism, complementary therapies, knowledge, pediatric nursing

## INTRODUCTION

Autism is a developmental disorder characterized by disorders in speech and social interaction skills that begin early, vary with age and developmental level, and have lasting effects throughout life.[1-3] Nurses working in pediatric clinics may provide care for children with autism, along with other children, throughout their professional lives. Hospital environments can be a more significant source of stress for children with autism. Diagnostic and therapeutic interventions, painful procedures, and environmental stimuli in the hospital can cause crises for these children. Therefore, nurses with no adequate knowledge of childhood autism may face specific challenges when providing care to children with autism. The knowledge, attitudes, and behaviors of nurses working in pediatric clinics towards autism are essential in terms of quality of care.[4-11]

Nurses' level of knowledge of autism affects not only nursing behaviors but also the attitudes of nurses.[12-16] However, a systematic review showed that healthcare workers have a

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moderate level of knowledge of autism, and they generally lack training.[17] Another study conducted with pediatric nurses revealed that 41% of nurses attributed the development of autism to supernatural causes.[18] It is apparent that such misconceptions will adversely affect pediatric nurses' approach toward children with autism.

Besides, pediatric nurses play an active role in the diagnosis and treatment of children with autism. In line with their knowledge of autism, they provide training and advice to children and parents with autism. One of these suggestions is the use of complementary therapy practices for children with autism. In studies on the use of CT in autism in the literature, the rate of use varies between 31% and 92%.[19,20] The most common alternative therapies include special diets (e.g., gluten- and casein-free) and biologically based therapies such as vitamin/mineral supplementation. In particular, gluten-free/casein-free diet, secretin, omega-3 fatty acid supplements, probiotics, glutathione, specific carbohydrate diet, SAM-E (S-adenosylmethionine), and melatonin are reported to be the most used ones.[21] There is a need for further studies in the literature about which CT methods are most frequently recommended by nurses working in pediatric clinics and why they recommend them.

This study, therefore, aimed to determine the knowledge levels and attitudes of nurses working in pediatric clinics about childhood autism and which CT methods they recommend to support children with autism.

## METHODS

### Study design and sampling

The study was descriptive research. Nurses working in pediatric clinics and using social media who were literate in Turkish comprised our study sample. Nurses working in the hospitals but not taking an active role in patient care and working in adult clinics were excluded. Relevant information and explanations about the study were added to the first part of the questionnaire, and the inclusion criteria were explained in detail. A total of 135 nurses who met the inclusion criteria and volunteered to participate in the study were included in the sample. Since all questions in the questionnaire had to be answered, there was no data loss. The research sample was completed two weeks after the number of filled questionnaires remained the same. The study was completed with the all individuals who could be reached on the dates when the research was continuing by not going to the sampling. According to the power analysis conducted considering the results obtained from 135 nurses in the research, the effect size of the study was found to be 0.30 (d=0.30) and the statistical power of the study was calculated as 95% at a 95% confidence interval.

### Data collection tools

Research data were collected through the Sociodemographic Information Form, the Societal Attitudes Toward Autism (SATA) Scale, and the Knowledge about Childhood Autism among Health Workers (KCAHW) Questionnaire.

*Sociodemographic Information Form*: It contains questions about the socio-demographic data of the nurses.

*Societal Attitudes Toward Autism Scale*: Developed by Flood, Bulgrin, and Morgan (2013), the scale is used to measure social attitudes towards individuals with autism. The factor analysis detected three subdimensions that are *Social Attitudes* (16 items), *Knowledge* (5 items), and *Personal Distance* (5 items). The Cronbach's alpha value of the scale was calculated to be 0.86.[22] The Turkish language version of the scale was adapted by Batum and Aydın.[23] The Cronbach α value for the validity and reliability of the Turkish version was calculated to be0.87.

*Knowledge about Childhood Autism among Health Workers Questionnaire*: Originally developed by Bakare et al. in the English language, this questionnaire consists of 19 items evaluating the information on four domains of autism.[24] The first domain consists of eight items and deals with inadequate social interactions among children. The second includes a single item on a symptom related to communication and language development. The third domain contains four items focusing on obsessive-compulsive, repetitive, and stereotypical behaviors that are characteristic of autism. The fourth domain consists of six items designed to assess nurses' knowledge of the neurodevelopmental nature of autism, possible comorbid conditions, and the prediction of its occurrence. The total scores in this questionnaire range from 0 to 19. Each item has three response options: Yes, No, and I don't know. Correct answers score1 point, while the other two answers score0 points. The last item, which evaluates the age of onset of autism, is scored as 0. Higher scores indicate a higher level of knowledge of autism. The Turkish version of the KCAHW questionnaire was adapted by Ozdemir et al.[25] The Cronbach α value of this questionnaire is 0.97 in the English version and 0.70 in the Turkish language version.

### Data collection

Research data were collected between August and October 2021. Data collection forms were transferred to Google Forms and a link was created to share the surveys. The created link was shared by the researchers on social media websites, including Facebook and Instagram, and the participants were invited to participate in the research.

Prior to data collection, a pilot application was conducted to test the comprehensibility of the questionnaires. Ten nurses were included in the pilot application and they answered all the questions in 10 to 20 minutes. After the pilot application, the nurses did not make any suggestions and no changes were made in the survey questions. Nurses who were included in the pilot application were excluded from the sample.

### Ethical considerations

A written approval from the ethics committee (E-60116787-020-90165) and written permissions from the authors for the use of the scales were obtained before starting the research. In addition, before displaying the questionnaire on the website, we presented some information on the subject and purpose of the study, as well as the time required to fill out the questionnaire so that we could educate the candidates on the process. In addition, the consent to participate was obtained by adding a section that stated "I agree to participate in this research of my own free will without any pressure or coercion: ( ) Yes, ( ) No". After selecting this option, the participants were able to move on to the next sections and send their answers.

### Data analysis

The research data were analyzed using the SPSS software package (version 21). The mean, standard deviation, number, and percentage values were calculated for the questions on the forms. When the parametric test assumptions were met, the Test of Significance of the Difference Between Two Means was used to compare independent group differences. When parametric test assumptions were not met, the Mann-Whitney U test was used to compare independent group differences. One-way ANOVA or Kruskal-Wallis H test was used when there were more than two groups. In addition, the relationships between continuous variables were examined by Spearman or Pearson correlation analyses. The Cronbach's alpha values were calculated for the scales used in the study. The power of the study was calculated using the statistical analysis software package Gpower v3.1.9.2. The results were evaluated at the 95% confidence interval, and a p-value lower than 0.05 ($p<0.05$) was considered significant.

## RESULTS

Introductory information about the participants is presented in Table 1. The age of the nurses participating in the study ranged between 24 and 51, and the mean age was 28.53±12.06. About 65.9% of the participants were women, 62.9% had a bachelor's

**Table 1. Descriptive characteristics of nurses**

| Socio-demographic Characteristics | Mean | | SD | |
|---|---|---|---|---|
| **Age** | 28.53 | | 12.06 | |
| | **Number** | **Percentage** | **SATA** | **KCAHW** |
| **Gender** | | | | |
| Female | 89 | 65.9 | t=0.550 | t=0.149 |
| Male | 46 | 34.1 | p=.592 | p=.884 |
| **Marital Status** | | | | |
| Married | 63 | 46.6 | t=1.430 | t=1.523 |
| Single | 72 | 53.4 | p=.176 | p=.152 |
| **Education** | | | | |
| High school | 10 | 7.4 | | |
| Associate degree | 2 | 1.5 | F=2.076 | F=2.157 |
| Bachelor's degree | 85 | 62.9 | p=0.168 | p=0.158 |
| Postgraduate/PhD | 38 | 28.2 | | |
| **Clinic** | | | | |
| Pediatric inpatient service | 91 | 67.4 | | |
| Pediatric surgery clinic | 17 | 12.5 | F=1.241 | F=1.574 |
| Pediatric ICU | 7 | 5.1 | p=0.311 | p=0.342 |
| Pediatric policlinic | 20 | 15 | | |

| Table 1. Continued | | | | |
|---|---|---|---|---|
| **Socio-demographic Characteristics** | **Mean** | | **SD** | |
| | **Number** | **Percentage** | **SATA** | **KCAHW** |
| **Work experience as nurse** | | | | |
| Less than 1 year | 21 | 15.5 | | |
| 1-5 years | 38 | 28.1 | F=2.235 | F=2.041 |
| 5-10 years | 42 | 31.1 | p=0.142 | p=0.174 |
| More than 10 years | 34 | 25.3 | | |
| **Work experience aspediatric nurse** | | | | |
| Less than 1 year | 44 | 32.5 | | |
| 1-5 years | 32 | 23.7 | F=2.712 | F=2.421 |
| 5-10 years | 38 | 28.1 | p=0.118 | p=0.124 |
| More than 10 years | 21 | 15,7 | | |
| **Has provided care for child with autism** | | | | |
| Never | 29 | 21.4 | F=2.076 | F=2.157 |
| Occasionally | 68 | 50.3 | p=0.168 | p=0.158 |
| Often | 33 | 28.3 | | |
| **Has recommended CT practice for children with autism** | | | | |
| Yes | 59 | 43.7 | t=1.872 | t=1.946 |
| No | 76 | 56.3 | p=.084 | p=.074 |
| **TOTAL** | 135 | 100 | | |

degree, and 67.4% worked in pediatric clinics. We found that 50.3% of the nurses occasionally provided care for a child with autism, and 43.7% recommended CT for the treatment of children with autism.

While the mean score of the SATA scale of the nurses participating in the study was 48.46±9.84, the mean score of the KCAHW questionnaire was 8.13±3.81. The mean scores of the subdimensions of the SATA scale was 7.93±2.49 at the lowest and 28.33±6.11 at the highest. The mean scores for the subdimensions included in the KCAHW questionnaire ranged between 1.73±0.96 and 3.86±1.95 (Table 2). There was a statistically significant relationship between the mean total scale scores of the nurses participating in the study (r=-0.924; p=0.000).

The data on CT practices recommended by the nurses participating in the study for children with autism are presented in Table 3. Exercise, special diets, and vitamin/mineral supplements ranked first among all CT practices.

| Table 2. Mean scale scores of nurses | | |
|---|---|---|
| | | **Mean±SD** |
| Scales | SATA | 48.46±9.84 |
| | KCAHW | 8.13±3.81 |
| KCAHW subdimensions | Relatively easy clinical observations | 3.86±1.95 |
| | The signs which require a longer observation time and detailed anamnesis | 1.73±0.96 |
| | The signs | 2.53±1.06 |
| SATA subdimensions | Societal attitude | 28.33±6.11 |
| | Knowledge | 12.2±2.88 |
| | Personal distance | 7.93±2.49 |

| Table 3. CT practices recommended by nurses | | |
|---|---|---|
| **CT practices** | **Incidence of CT recommendation by nurses** | |
| | **n** | **%** |
| Special diets | 55 | 40.7 |
| Exercise/Physical activity | 57 | 42.2 |
| Probiotic foods and drinks | 12 | 8.8 |
| Vitamin/mineral supplements | 31 | 22.9 |
| Meditation | 13 | 10 |
| Yoga | 10 | 7.4 |
| * Nurses were able to mark more than one option. | | |

## DISCUSSION

Our study investigated the knowledge of nurses working in pediatric clinics about childhood autism, their attitudes toward the condition, and the CT methods they employed to support children with autism. We determined that half of the nurses participating in the study occasionally provided care for children with autism, and nearly half of them recommended CT practices. It was found that nurses most frequently recommended exercise, special diets, and vitamin/mineral supplements. The nurses' knowledge of childhood autism was above average, and the level of negative attitudes toward autism was low among our participants. We can suggest that the level of knowledge about childhood autism significantly affects the social attitudes towards autism, and as the level of knowledge increases, the negative attitudes decrease.

Corsano et al.[4] investigated the knowledge and experiences of pediatric nurses about autism, reporting that six out of ten nurses who participated in their study had previous experience with an individual with autism. However, in our study, this rate was slightly higher. There are studies in the literature reporting that having experience with an individual with autism has some effect on the nurses' level of knowledge about autism.[4,26] In contrast, others report that it does not affect the level of knowledge.[27,28] In our study, we found that having experience of nursing care for children with autism in the clinics had no significant effect on nurses' level of knowledge about the condition. There are many factors affecting an individual's acquisition of information. In addition to encountering individuals with autism, factors such as the amount of time nurses spend with them, their interest in autism, and their learning styles can be effective. It is thought that encountering people with autism may not be enough to learn the necessary information about autism.

Previous research on this matter has reported that the knowledge level of pediatric nurses about autism is determined by variables such as age and professional experience. A study reported that nurses' prior knowledge of autism CT from their experiences in the care they provided to children with autism during their professional life.[4] In this case, this studies show that it is inevitable for nurses and other healthcare professionals to hold now-abandoned or false beliefs about autism.[4,18] In this study, contrary to the literature, we found that work experience and the length of service in pediatric clinics had no effect on their knowledge, which could help raise awareness among nurses and abandon traditional fallacies about autism.

The level of knowledge about childhood autism among our participants was found to be above average. A detailed review of previous research conducted with health workers and nurses indicated that nurses generally had false beliefs about autism and their level of knowledge varied from low to moderate.[13,18,29] Similarly, previous studies in Türkiye reported that the level of knowledge of health workers varied according to occupational groups.[30,31] There are studies in the literature that clearly indicate that the level of knowledge about autism affects individuals' attitudes toward autism.[12-16] The correlation analysis performed in this study determined that the knowledge level of pediatric nurses was related to their attitudes toward individuals with autism at a very high level. Having accurate information about children with autism may affect their attitudes toward individuals with autism and their caregiving consultations. For this reason, it is essential to determine the level of knowledge of pediatric nurses, as well as all other health professionals, to eliminate deficiencies and correct their mistakes.

Almost half of the nurses participating in the study recommended CT practices for children with autism. It is frequently stated in the literature that parents use CT practices for their children with autism. However, there is no study on what pediatric nurses think about this issue and what they recommend. However, as reported in this study, the majority of pediatric nurses occasionally or frequently work with children with autism in their clinics. In this process, it is extremely important to determine what suggestions they make to families and children to the best of their knowledge. In our study, we found that nurses suggested six different CT practices in total, with exercise being the most frequently recommended one. Tarr et al.[32] reported that physical activity or exercise has a moderate effect as a potential treatment for stereotypic behaviors in children with autism. He also presented data on exercise in autism in many studies. This suggests that exercise can be used in autism. However, it is very important for nurses to follow the literature on this subject and to guide them in light of the information they obtain from publications with high levels of evidence. A study published in Türkiye in 2021 examined the CT practices preferred by families for their children with autism and reported that there were twelve practices in total. The most frequently preferred practices by parents were spiritual relaxation techniques (prayers) (69.8%), followed by probiotic supplements (49.3%), and vitamin supplements (38.4%). Parents reported that these practices had positive effects on their children's communication, behavior, learning and health.[33] CT practices can be effective in providing positive development in children with autism. Therefore, it is imperative for pediatric nurses to obtain the necessary information on such practices as well as on autism in general.

## CONCLUSION

The level of knowledge on childhood autism among our participants was found to be above average. In addition, in this study, the knowledge level of pediatric nurses was related to their attitudes towards individuals with autism at a very high level. So, it is recommended to prepare a guide regarding autism and CT suggested by nurses. It is recommended to plan the necessary interventions to improve the knowledge and attitudes of pediatric nurses about autism and to prepare a guide about CT to be used by nurses.

### Limitations

Since the data were collected through social media, information about the hospital and service, such as bed capacity and number of patients, could not be reached. This is the most important limitation of the study. Another limitation of the study is its descriptive design.

### Ethical approval

This study has been approved by the Pamukkale University Non-Invasive Clinical Research Ethics Committee (approval date 17.08.2021, number E-60116787-020-90165). Informed consent was not required because of the retrospective design.

### Author contribution

Concept: ÇE, TT; Design: ÇE; Data Collection or Processing: ÇE, TT; Analysis or Interpretation: ÇE, TT; Literature Search: ÇE; Writing: ÇE, TT. All authors reviewed the results and approved the final version of the article.

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### Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

# Mortality and short-term morbidities of multiple birth neonates hospitalized in a tertiary neonatal intensive care unit

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## ABSTRACT

**Objective:** Multiple pregnancies are associated with an increased risk of adverse maternal and neonatal outcomes, especially those associated with prematurity. The purpose of this study was to assess the mortality and short-term morbidity of infants born from multiple pregnancies and hospitalized in neonatal intensive care units.

**Methods:** The medical records of women who gave birth to multiple neonates over four-year period and their children were retrospectively analyzed. The study examined neonatal outcomes, specifically mortality, and short-term morbidity, during hospitalization.

**Results:** The study included 220 neonates from 126 multiple pregnancies (three triplets and 123 twins). The preterm birth rate was 97%. Presentation anomalies, cesarean section rates, assisted reproductive techniques (ART), congenital anomalies, and antenatal corticosteroid administration were statistically higher in multiple births compared to singleton births. In multiple pregnancies, the rates of spontaneous, in-vitro fertilization, and intrauterine insemination were 73%, 21.5%, and 5.5%, respectively. There were 78.5% dichorionic diamniotic pregnancies, 14.5% monochorionic diamniotic pregnancies, 4.7% monochorionic monoamniotic pregnancies, and 2.3% trichorionic triamniotic pregnancies detected. Monochorionic pregnancies were associated with lower birth weight and longer duration of total parenteral nutrition (1808±548 vs. 1994±524g, p=0.02, and 12.6±9.9 vs. 8.3±7.1days, p=0.005, respectively). Significantly higher rates of monochorionic placentation, higher maternal age, and maternal disease frequency were observed in ART multiple pregnancies (p=0.001, p=0.01 and p=0.02, respectively. Birth order had no significant effect on perinatal outcomes. Male infants were discharged more frequently with the diagnosis of small for gestational age (32.5% vs. 14.5%, p=0.003). Fourteen infants were lost, including four in utero, six due to extreme prematurity, one due to Trisomy 18, three due to sepsis and necrotizing enterocolitis in the neonatal period.

**Conclusion:** Multiple pregnancy and associated complications, especially prematurity and low birth weight, are increasing. Both antenatal and postnatal approaches need to be improved and specialized to improve neonatal outcomes.

**Keywords:** In vitro fertilization, morbidity, mortality, multiple pregnancy, neonate, twins

## INTRODUCTION

Over the last two decades, the incidence of multiple births has increased due to the widespread use of assisted reproductive techniques (ART).[1] This is especially true in high-income and middle-income countries, where infertility, maternal age, and delay in childbearing have increased. Twin pregnancies account for between 2-4% of all births. Multiple births occur in approximately 20% of naturally conceived pregnancies, compared to 40-60% of in-vitro fertilization (IVF) pregnancies.[2] The increased number of fetuses and the resulting reduction in gestational age at birth are associated with increased maternal, fetal, and neonatal morbidity and mortality. The majority of maternal complications are caused by preeclampsia, pregnancy-

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induced hypertension, gestational diabetes, cesarean delivery, and postpartum bleeding. On the other hand, the incidence of preterm births and prematurity-related morbidities, such as small-for-gestational-age (SGA) infants, respiratory distress syndrome (RDS), risk of cerebral palsy, as well as congenital defects and malpresentations, is on the rise.[3,4] Complications caused by multiple pregnancies are directly proportional to the number of fetuses. Chorionicity and zygosity also play a role in fetal morbidity and mortality, which is greater in monochorionic twins than in dizygotic twins and singletons.[5] In this study, the perinatal and short-term neonatal morbidity and mortality of babies born to multiple pregnancies and hospitalized in a hospitalized in a tertiary neonatal intensive care unit (NICU) were examined and compared to those born to singleton pregnancies.

## MATERIAL AND METHODS

Two hundred and twenty neonates from 126 multiple pregnancies who were admitted to the NICU of Balıkesir Atatürk City Hospital between October 2018 and October 2022 were included in the study. The medical records of the patients and their mothers were retrospectively reviewed. Data including maternal age and diseases, parity, presence of discordance (i.e. >15% of weight difference between twins), gestational age, gender, position (cephalic, breech or transverse) and type of birth (cesarean section/spontaneous vaginal delivery), chorionicity and amniocity, history of ART, antenatal corticosteroid usage, intrauterine or postnatal death, APGAR scores, cause of hospitalization, duration of NICU stay, mechanical ventilation and total parenteral nutrition (TPN), morbidities including RDS and need for surfactant treatment, necrotizing enterocolitis (NEC), patent ductus arteriosus (PDA), retinopathy of prematurity (ROP), intracranial hemorrhage (ICH), bronchopulmonary dysplasia (BPD), late onset sepsis (LOS), surgical diseases and history of any operation, transfusion and phototherapy were recorded. Standard echocardiography, transfontanelle, and abdominal ultrasonography were used to detect congenital malformations, while magnetic resonance imaging was utilized in suspicious cases.

Preterm birth was defined as birth before 37 weeks of gestation. An infant was classified as SGA if the birth weight was less than 10%, as appropriate for gestational age (AGA) if the birth weight was between 10% and 90%, and as large for gestational age (LGA) if the birth weight was greater than 90% of the weight expected for the gestational age.[6] Small for gestational age, AGA, and LGA infants were investigated at both hospitalization and discharge. Late preterm births were defined as infants born between 34+0/7 and 36+6/7 weeks gestation and preterm births were defined as those occurring between 37+0/7 and 38+6/7 weeks.[7]

In the event that only one sibling was hospitalized, any significant differences in birth order, gender, and birth weight were investigated. The effects of gender, birth order, chorionicity, IVF, and natural conception on the results were examined. The control group consisted of 200 gestational age-matched babies of singleton pregnancies who were hospitalized in the NICU and two groups were compared. Informed consent was not required because of the retrospective design.

Ethical approval for the study was obtained from Bandırma Onyedi Eylül University Non-invasive Clinical Research Ethics Committee in line with the principles outlined in the Second Declaration of Helsinki (approval number: 2022-107).

### Statistical analysis

Data were analyzed using SPSS software version 21 (SPSS Inc. Chicago, Illinois, USA) program. The Shapiro-Wilk test was performed to test the normality of the distribution of the data. Categorical data were presented with n and %, and numerical data with mean ± standard deviation if normally distributed, and median interquartile range (IQR) if non-normally distributed. Continuous variables were evaluated using the Student's t-test or Mann-Whitney U test, depending on the distribution characteristics of the data, and categorical variables were evaluated with the chi-square or Fisher exact test. The Kruskal-Walllis test was used in the comparison of three independent groups with non-normally distributed data. A p-value <0.05 was considered as statistically significant. The statistical power of the study was calculated using G Power 3.1.9.7 program. With the effect size of 0.55 and alpha error 0.05, using mean birth weight and standard deviations in monochorionic and dichorionic pregnancies, the power of the study was found to be 0.97. With the alpha error of 0.05 and using proportions of low birth weight and anomalies of presentation in multiple and singleton pregnancies, the power of the study was detected as 0.99 and 0.98, respectively.

## RESULTS

The total number of infants born in our hospital was 15500, and 279 (1.8%) were from multiple pregnancies. Two hundred and twenty of 279 babies born to multiple pregnancies in our hospital were admitted to the NICU, representing 79% (126 multiple pregnancies). The remaining 59 (21%) infants did not require hospitalization. The proportion of infants born and hospitalized with multiple pregnancies during the same period was 9% of all hospitalized infants. Three of the multiple pregnancies were triplets, while the remaining 123 were twin pregnancies. The most common reason for hospitalization among 200 (91%) neonates was respiratory distress; other

| Table 1. Demographical and clinical findings of babies from multiple and singleton pregnancies (n, mean [± std] or median [IQR]) | | | |
|---|---|---|---|
| | **Multiple pregnancies n=220** | **Singleton pregnancies n=200** | **p value** |
| Gestational age(weeks) | 34 (3) | 34 (4) | 0,95 |
| Gender | | | |
| Female | 121 | 84 | 0,02 |
| Male | 99 | 116 | |
| Birth weight (g) | 1980 (617) | 2150 (900) | 0,13 |
| Maternal age(yrs) | 30(8) | 31(8) | 0,51 |
| Maternal disease | 77 | 80 | 0,40 |
| Maternal parity | | | |
| Primipar | 114 | 120 | 0,08 |
| Multipar | 106 | 80 | |
| Presentation | | | |
| Cephalic | 163 | 182 | **<0,001** |
| Breech | 50 | 18 | |
| Transverse | 7 | | |
| Antenatal kortikosteroids | 122 | 142 | **0,006** |
| Type of birth | | | |
| Vaginal delivery | 26 | 58 | **<0,001** |
| Cesarean section | 194 | 142 | |
| Apgar scores | | | |
| 1 min (median) | 8 | 8 | 0,13 |
| 5 min (median) | 9 | 9 | |
| Type of fertility | | | |
| Spontaneous | 151 | 196 | **<0,001** |
| IVF | 56 | 4 | |
| IUI | 13 | - | |
| Extremely low birth weight | 15 | 14 | 0,91 |
| Low birth weight at birth | 36 | 16 | **0,04** |
| Low birth weight at discharge | 53 | 44 | 0,67 |
| RDS | 99 | 98 | 0,55 |
| Surfactant use | 90 | 97 | 0,22 |
| NEC | 8 | 4 | 0,18 |
| ICH | 16 | 8 | 0,28 |
| ROP ≥ stage 2 | 11 | 14 | 0,43 |
| PDA | 21 | 32 | 0,10 |
| Late neonatal sepsis | 66 | 60 | 0,81 |
| Surgery | 4 | 6 | 0,78 |
| Congenital anomalies | 34 | 8 | **<0,001** |
| Mechanical ventilation (days) | 4 (6) | 4 (8) | 0,31 |
| TPN (days) | 7 (7) | 7 (10) | 0,93 |
| Hospitalization (days) | 18 (17) | 18 (22) | 0,65 |
| Transfusion | 44 | 54 | 0,12 |
| Phototerapy | 66 | 100 | **<0,001** |
| Death | 10 | 6 | 0,47 |

IVF: In-vitro fertilization, IUI: Intrauterine insemination, RDS: respiratory distress syndrome, NEC: Necrotizing enterocolitis, ICH: Intracranial hemorrhage, ROP: Retinopathy of prematurity, PDA: Patent ductus arteriosus, TPN: Total parenteral nutrition

reasons included feeding problems, hypoglycemia, and jaundice. The incidence of maternal morbidity was 35%, with gestational diabetes, intrahepatic cholestasis of pregnancy, preeclampsia, and hypertension being the most prevalent diseases. At birth, neonates with a history of maternal diseases had significantly lower gestational age (32.5±3.0 vs. 33.5±2.5, p=0.04) and first minute Apgar scores (7.2±1.9 vs. 7.8±1.0, p=0.03) but higher rates of extremely low birth weight (12.2% vs. 3.7%, p=0.02). Table 1 displays the demographic and clinical characteristics of the hospitalized multiple and singleton neonates.

Only 15 (7%) of the babies were born at term, 13 were early term births and 205 (93%) of the babies born and hospitalized after multiple pregnancy in our study were born preterm. Late preterm birth was detected in 101 (46%) cases. The most prevalent malformations were renal anomalies; hydronephrosis was identified in 23 patients, while ectopic kidney and renal agenesis were identified in two patients. Four patients with retinopathy of prematurity underwent laser photocoagulation; four patients required surgery: two for NEC, one for Hirschsprung's disease, and one for inguinal hernia.

In multiple pregnancies, the number and frequency of spontaneous, IVF, and intrauterine insemination were 92 (73%), 27 (21.5%), and 7 (5.5%), respectively. There were 99 (78.5%), 18 (14.5%), 6 (4.7%), and 3 (2.3%) dichorionic diamniotic, monochorionic diamniotic, monochorionic monoamniotic, and trichorionic triamniotic pregnancies, respectively. Monochorionic pregnancies were associated with statistically lower weight and longer duration of TPN compared to dichorionic pregnancies (1808±548 vs. 1994±524g, p=0.02, and 12.6±9.9 vs. 8.3±7.1 days, p=0.005, respectively). Monochorionic pregnancies resulted in a longer NICU stay compared to dichorionic pregnancies, but the difference was not significant (26.6±22.8 vs. 21.7±18.5 days, p=0.05). Two of the three trichorionic triamniotic triplet pregnancies were induced by IVF, while one was conceived naturally. Discordance was observed in 32 pregnancies (25.5%), eight of which had monochorionic placentation. When the outcomes of ART and spontaneous multiple pregnancies were compared, monochorionic placentation (28.5% vs. 8.8%, p=0.001), maternal age (31.5±5 vs. 29±5, p=0.01), and maternal disease frequency (49.1% vs. 30.5%) were significantly higher in ART multiple pregnancies. There was no statistical difference in birth weight, mortality, congenital anomalies, gestational age, or prematurity-related morbidities. The birth order had no statistically significant effect on perinatal outcomes. The study also found that male infants were discharged more frequently with the diagnosis of SGA than female infants (32.5% vs. 14.5%, p=0.003).

In 49 pregnancies, only one of the twins was hospitalized, of whom 60% was male, but there was no statistically significant difference in terms of birth weight and gender. Fourteen babies died during hospitalization. Seven babies were lost in the early neonatal period, six of them were lost due to extreme prematurity and the other patient was lost due to Trisomy 18. The other three babies died due to sepsis and necrotizing enterocolitis in the late neonatal period. Three of the four babies with intrauterine exitus were the result of monochorionic pregnancies, two of them had twin-to-twin transfusion syndrome (TTTS), one had twin anemia polycythemia syndrome (TAPS) and the other intrauterine exitus was one of the trichorionic triamniotic triplets.

## DISCUSSION

Compared to singletons, multiple pregnancies are associated with higher rates of presentation anomalies, cesarean section rates, IVF births, congenital anomalies, and antenatal corticosteroid administration. Neonates from monochorionic pregnancies were recorded to have lower weight, and longer TPN duration than dichorionic pregnancies, and monochorionic placentation, maternal disease frequency, and maternal age were significantly higher in IVF multiple pregnancies. Males were also more frequently discharged SGA.

Multiple pregnancies are associated with a significantly higher risks of maternal and neonatal complications when compared to singleton pregnancies, according to numerous studies. Increasing preterm births, postpartum bleeding, premature rupture of membranes, hypertensive disorders, diabetes, cesarean section, advanced maternal age, and low birth weight exacerbate perinatal morbidity and mortality.[8] It is known that perinatal mortality is six times higher in multiple pregnancies, and that preterm birth and birth weight are the most influential factors in infant morbidity and mortality.[9] Some studies have found that the preterm birth rate for twin pregnancies ranges from 31-44%, with a maximum of 63%.[10,11] In our study, the mean gestational age of infants born and hospitalized with a multiple pregnancy was determined to be 33.1± 2.7 weeks; only 8.8% of the infants were born at term, and morbidities associated with prematurity, particularly RDS, surfactant use, GNS, and ICH, were frequently observed.

In a meta-analysis by Kalikkot et al.[12], RDS, BPD, any ICH, and bacterial sepsis were found to be significantly lower in twin and triplet preterm births compared to singletons, whereas pulmonary hemorrhage and severe ICH were detected much more frequently, and there was no difference between the groups for severe ROP and NEC. Santana et al.[13] found that twin pregnancy was directly associated with low birth weight, higher incidence of noncephalic presentation, particularly for the second twin, increased risk of congenital anomalies, and lower 5-minute Apgar scores. A second meta-analysis demonstrated that twin births were associated with higher rates of preterm

birth, low birth weight, stillbirth, early neonatal death, and NICU admission.[9] In our study, multiple pregnancies were associated with higher rates of low birth weight, congenital malformations, and anomalies of presentation compared to singleton pregnancies; however, 1-5 min Apgar scores, RDS, NEC, ICH, ROP stage 2, LOS, mechanical ventilation, and hospitalization durations were comparable.

For years, the optimal mode of delivery in multiple pregnancies has been debated, and second twins were thought to have worse outcomes, particularly with vaginal delivery, which led to an increase in cesarean rates in multiples, with a reported prevalence of 34-82%.[14-16] Amniocity and fetal presentation are the primary determinants of mode of delivery. In the case of cephalic presentation of the presenting twins, diamniotic twins are typically delivered vaginally if there is no standard indication for cesarean delivery.[17,18] For diamniotic twins with a noncephalic-presenting twin, monoamniotic twins, and pregnancies with standard obstetric indications for cesarean birth[17], cesarean birth is the preferred mode of delivery. In a very large study involving 1398 women (2795 fetuses) randomly assigned to planned cesarean delivery and 1406 women (2812 fetuses) randomly assigned to planned vaginal delivery, Barrett et al.[15] determined that there was no advantage to planned cesarean delivery over planned vaginal delivery for the delivery of twins between 32 and 38 weeks of gestation, if the first twin was in the cephalic presentation. Despite the evidence, cesarean section is the preferred method of delivery in the majority of multiple pregnancies, as shown in the present study with a very high rate of 88%, which was significantly higher than that of singleton pregnancies (71%), which may be due to a significantly higher incidence of presentation anomalies and higher rates of emergency/repeat cesarean section in multiple pregnancies. In the case of a non-vertex second twin and a prolonged interval between twin deliveries, the likelihood of a vaginal-cesarean (combined) delivery is increased.[19] In our study, combined delivery was performed in two twin pregnancies; the second twin had lower APGAR scores and a longer duration of mechanical ventilation than the first twin born by vaginal delivery; however, in the other pregnancy, the first twin had been expelled on the first day of life due to extreme prematurity. According to studies examining the effect of birth order on perinatal outcomes, the second twin has a higher risk of perinatal mortality rates as well as lower Apgar scores and birth weight.[9,11,20] In contrast, our study found no correlation between birth order and neonatal outcomes.

Multiple pregnancies are associated with greater alterations in maternal hemodynamics than singleton pregnancies. Gestational hypertension and preeclampsia are significantly more prevalent in multiple births. Multiple pregnancies have a higher incidence of acute maternal morbidity and intrapartum/postpartum complications than singleton pregnancies.[21,22] In this study, 39% of multiple pregnancies were associated with maternal morbidity, with gestational diabetes, intrahepatic cholestasis of pregnancy, preeclampsia, and hypertension being the most prevalent. In contrast to previous research, our study found no statistically significant difference between the prevalence of maternal diseases in multiple and singleton pregnancies. This can be attributed to the fact that our hospital is a perinatal center and the region's high-risk singleton and multiple pregnancies, as well as those with a high incidence of maternal diseases, are monitored in our institution.

Chorionicity is one of the most significant predictors of outcome in multiple pregnancies. Compared to dichorionic twins, monochorionic twins have a significantly higher risks of intrauterine morbidity and mortality.[23] Multiple pregnancies are associated with an increased risk of intrauterine death, unexplained stillbirth, and cerebral palsy later in life.[24,25] The majority of fetal complications, especially in multiple pregnancies requiring invasive treatment, are caused by intraplacental vascular connections between the fetal circulations in monochorionic placentation. Approximately 30% of monochorionic diamniotic pregnancies are known to be susceptible to complications, including twin-to-twin transfusion syndrome (TTTS), selective intrauterine growth restriction, twin anemia-polycythemia sequence (TAPS), twin reversed arterial perfusion, conjoined twins, fetal death, or anomalies.[26] Twin-to-twin transfusion occurs in 15% of monochorionic diamniotic pregnancies and is fatal in up to 80% of untreated cases.[27] In our study, TTTS was diagnosed in three of the monochorionic pregnancies, and one of the twins in two of the TTTS pregnancies died in utero. Another two monochorionic pregnancies in which one of the twins died in utero were diagnosed with TAPS. In addition, our study found that babies from monochorionic pregnancies had a lower birth weight, a longer TPN duration and a nonsignificantly longer NICU stay.

In-vitro fertilization in twins is associated with increased gestational diabetes, hypertensive disorders of pregnancy, preterm birth, and prolonged ventilation in newborns, compared to spontaneously conceived multiple pregnancies.[28] In the IVF group, there are also higher risks of cesarean section and a lower gestational age at birth.[29] A large retrospective cohort found that women with IVF pregnancies were older and had a higher proportion of nulliparity, which was associated with a slight increase in preterm birth and NICU admission. However, there were no differences between IVF/intracytoplasmic sperm injection and spontaneous dichorionic diamniotic pregnancies in terms of spontaneous preterm birth, gestational diabetes mellitus, pregnancy-induced hypertension, preeclampsia,

intrahepatic cholestasis of pregnancy, and birthweight.[30] The current study revealed that monochorionic placentation, frequency of maternal diseases and maternal age were significantly higher in ART multiple pregnancies; and there was no statistically significant difference in birth weight, mortality, congenital anomalies, gestational age, and prematurity-related morbidities.

## CONCLUSION

Multiple pregnancies carry a high risk for adverse perinatal outcomes, and their incidence is increasing. Due to preterm birth and growth restriction, twins, triplets, and even quadruplets are frequently hospitalized in NICUs and at a high risk for morbidity and mortality associated especially with premature birth.

### Ethical approval

This study has been approved by the Bandırma Onyedi Eylül University Non-invasive Clinical Research Ethics Committee (approval date 13.09.2022, number 2022-107). Informed consent was not required because of the retrospective design.

### Author contribution

Surgical and Medical Practices: MÖ, AÇ, MB, GV; Concept: MÖ, AÇ, MB, GV; Design: MÖ, AÇ, MB, GV; Data Collection or Processing: MÖ, AÇ, MB, GV; Analysis or Interpretation: MÖ, AÇ, MB, GV; Literature Search: MÖ, AÇ, MB, GV; Writing: MÖ, AÇ, MB, GV. All authors reviewed the results and approved the final version of the article.

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### Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

# The effect of subcutaneous immunoglobulin replacement therapy on serum IgG levels in patients with primary immunodeficiency

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## ABSTRACT

**Objective:** In a large group of patients with primary immunodeficiency (PID), immunoglobulin replacement therapy is critical for infection control. There are two main methods of immunoglobulin replacement intravenous (IVIG) and subcutaneous (SCIG). The aim of this study was to determine the efficacy of SCIG by comparing IgG levels and frequency of infections obtained during SCIG replacements in patients with PID with those obtained during IVIG administration.

**Method:** Immunoglobulin levels of 28 patients who were followed up in our clinic with a diagnosis of PID and who started IVIG replacement and switched to SCIG replacement after follow-up, were evaluated retrospectively. Serum IgG levels and frequency of infections before starting immunoglobulin treatment, the previous year of IVIG before starting SCIG replacement, and during the first six months, second six months, and second year of SCIG replacement were compared.

**Results:** The mean age of all the patients that received SCIG was 10.5 years (min 15 months, max 23 years) and eleven of the patients were female. The mean serum IgG level of the patients before starting immunoglobulin replacement was 701±383 mg/dl, and for the final year they received IVIG replacement before switching to SCIG replacement it was calculated to be 900±342 mg/dl. The mean value was found to be 1082±312 mg/dl in the first six months after the initiation of SCIG, 1102±287 mg/dl in the second six months, and 1145±311 mg/dl in the second year. Serum IgG levels of the patients were significantly higher during IVIG and SCIG replacement than before treatment ($p<0.05$). Serum IgG levels during the first six months, second six months, and second year of SCIG treatment were significantly higher than levels during IVIG treatment ($p=0.000$, $p=0.003$, and $p=0.002$, respectively).

**Conclusion:** Compared to IVIG replacement, significantly higher and more stable serum IgG levels can be obtained with SCIG replacement. This is expected to ensure improved outcomes in the management of infections in PID patients.

**Keywords:** IgG levels, intravenous immunoglobulin replacement, subcutaneous immunoglobulin replacement

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## INTRODUCTION

Primary immunodeficiency (PID) is a clinically heterogeneous disease caused by genetic defects that affect the development and function of various components of the immune system. The overall incidence of PID is estimated to be around 1:10,000, with the majority of cases presenting in childhood.[1] It is known that this frequency is much higher in countries with a high rate of consanguineous marriages, such as Türkiye. The number of genetic mutations responsible for primary immunodeficiency is increasing daily as a result of developments in genetic diagnosis. Primary immunodeficiency is caused by 485 genetic mutations classified by the IUIS (International Union of Immunological Societies) in 2022.[2] More than half of PIDs are associated with impaired humoral immunity.[3,4]

As a biological product, immunoglobulin G (IgG) is the most important immune molecule modulating the immune system. It is utilized for its anti-inflammatory and immunomodulatory properties, in addition to its use in the treatment of infections. Therapeutic immunoglobulin replacement was first used in 1952 by Ogden Carr Bruton in a patient with X-linked agammaglobulinemia.[5,6] Intravenous immunoglobulin replacement therapies in the modern sense came to the fore with the availability of intravenous immunoglobulin preparations in 1981, and eventually became the standard treatment for many PIDs. In recent years, subcutaneous immunoglobulin replacement therapy (SCIG-RT) and subcutaneous immunoglobulin replacement (fSCIG) facilitated with hyaluronidase enzyme have emerged as reliable alternatives to IVIG administration in adults and children with PID. The main advantage of IVIG replacement therapy (IVIG-RT) over SCIG-RT is that it can be administered in much larger volumes, allowing serum IgG levels to reach peak serum concentrations much faster.[7] This may make it preferable in patients who need high-dose treatment for acute infection or in patients with autoimmune disease who want to benefit from the immunomodulatory effect. Furthermore, it may allow for less frequent administration. The prolonged infusion period, the need for trained healthcare professionals and a hospital setting, the requirement of IV access, and the increased risk of systemic adverse effects are the downsides of the IVIG-RT.[7] Less systemic adverse effects, more consistent IgG levels, and ease of administration at home by the patient or the patient's family members are the benefits of SCIG-RT.[7] As a result, it improves quality of life and reduces dependence on hospitals. Furthermore, some children and adolescents may refuse frequent and multiple injections. Individuals with extensive skin lesions, severe thrombocytopenia, or coagulopathy may not be suitable for SCIG administration.[8] Therefore, it is recommended to adopt a patient-centered approach when choosing SCIG or IVIG and to consider the patient's lifestyle, needs, treatment compliance, clinical picture, and side-effect profile. SCIG and IVIG therapies can be alternated occasionally if the above-mentioned circumstances change. The purpose of this study was to compare the serum immunoglobulin-G levels and frequency of infections in our patients with PID who switched to SCIG-RT while receiving IVIG-RT and to determine the efficacy of SCIG-RT.

## MATERIAL AND METHODS

The immunoglobulin levels of 28 patients who were followed up in our clinic with the diagnosis of primary immunodeficiency and were started on IVIG replacement and then switched to SCIG replacement during the follow-up were evaluated retrospectively. SCIG-RT as an alternative treatment option and its characteristics were explained to patients with primary immunodeficiency who were receiving IVIG-RT in our clinic, and patients who wanted to continue their treatment subcutaneously were included in the study. Patients who wanted to switch back from SCIG-RT to IVIG-RT treatment and those who did not continue their clinical follow-up were excluded from the study. During this time, the patients received IVIG-RT at intervals of 3–4 weeks with a maintenance dose of 400-600 mg/kg, and we assessed the pre-infusion serum IgG levels before every second infusion as part of our outpatient follow-up protocol. Since SCIG-RT is administered by the individuals at home at 1- or 2-week intervals in a divided amount of the same dose as IVIG-RT, serum IgG levels in these patients were assessed every 3 months during routine controls. The average IgG levels before the start of immunoglobulin treatment, the previous year of IVIG before starting SCIG-RT, and during the first six months, second six months, and second year of SCIG-RT were compared. Statistical analysis was performed by using the SPSS 21 program. The Wilcoxon test was used to compare the mean values of serum IgG levels and the frequency of infections and $p<0.05$ was considered statistically significant.

### Study design and ethical approval

This retrospective cross-sectional study was approved by SBU İzmir Dr. Behçet Uz Education and Research Hospital Clinical Research Ethics Committee in 2022 (Decision No: 2022/22-10).

## RESULTS

Twenty-eight patients who were followed up in our clinic with the diagnosis of PID and who started IVIG replacement and then switched to SCIG replacement after follow-up were included in the study. Seventeen of the patients were male and the mean age was 10.5 years (the youngest was 15 months old, the oldest was 23 years old). The baseline characteristics of the patients

| Table 1. Patient baseline characteristics | |
|---|---|
| **Gender** | |
| Female (n-%) | 11 (39.3) |
| Male (n-%) | 17 (60.7) |
| **Age (years)** | |
| Mean (SD) | 10.5±4.7 |
| **Age of initiation to IVIG-RT (years)** | |
| Mean (SD) | 6.2±4.0 |
| **Age of initiation to SCIG-RT (years)** | |
| Mean (SD) | 8.3±5.2 |
| Diagnosis | |
| Common Variable Immunodeficiency (CVID) | 11 (39.3) |
| Unclassified Hypogammaglobulinemia | 4 (14.2) |
| Ataxia-Telangiectasia (AT) | 3 (10.7) |
| Hyper IgE Syndrome | 3 (10.7) |
| X-linked Agammaglobulinemia (XLA) | 3 (10.7) |
| Transient Hypogammaglobulinemia | 2 (7.1) |
| DiGeorge Syndrome | 1 (3.5) |
| WD Repeat-Containing Protein 1 mutation (WDR-1) | 1 (3.5) |

are shown in Table 1. The average duration of IVIG-RT prior to SCIG-RT was 35 months and the average duration of SCIG-RT was 15 months. The youngest patient who began SCIG-RT was 7 months old, while the oldest was 22 years old. The mean serum IgG level of the patients before the immunoglobulin replacement was 701±383 mg/dl and the mean serum IgG level of the previous 1 year before switching to SCIG-RT was 900±342 mg/dl. As a result, the amount of monthly dose was similar for both types of replacement therapy. Mean serum IgG values in the first 6 months after SCIG initiation were found to be 1082±312 mg/dl, 1102±287 mg/dl in the second 6 months, and 1145±311 mg/dl in the second year (Figure 1). While the patients were receiving IVIG and SCIG replacement, the mean serum IgG levels of the patients were significantly higher than before treatment ($p<0.05$) (Figure 1). The serum IgG levels in the first 6 months, the second 6 months, and the second year of SCIG-RT were significantly higher than the mean levels while taking IVIG ($p=0.000$, $p=0.003$, $p=0.002$, respectively) (Table 2). The frequency of infections in each period of immunoglobulin replacement therapy was statistically significantly lower than in the pre-treatment period. When the frequency of infections during IVIG-RT was compared to the first and second year of SCIG-RT, the frequency of infections was lower during the SCIG-RT application period, but there was no significant difference in the frequency of lower respiratory tract infections (Table 2).

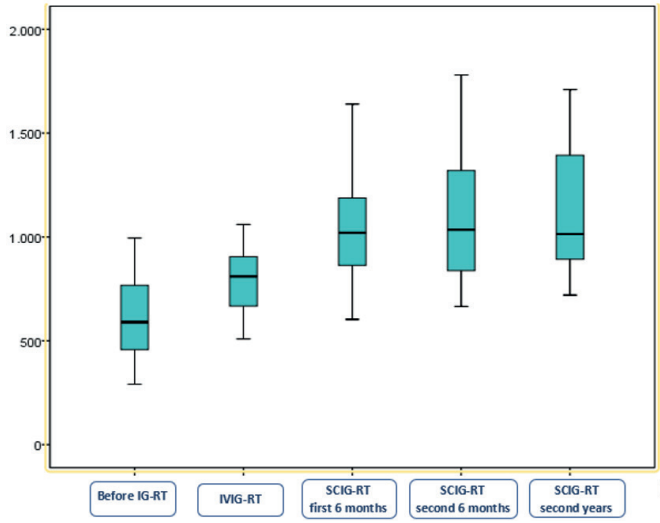


**Figure 1.** Serum IgG levels according to periods of replacement treatment

## DISCUSSION

Our findings show that the patients who received SCIG-RT had higher IgG trough levels than those who received IVIG-RT. These findings could be explained by the fact that the pharmacokinetics of IgG differ when smaller doses are given more frequently versus large boluses given monthly. In our study, SCIG therapy was associated with lower peaks and higher IgG troughs, which is consistent with the literature.[9] Patients with primary antibody deficiency are particularly susceptible to bacterial infections, especially affecting the respiratory and gastrointestinal tracts. These patients are usually scheduled for life-long IGRT to prevent these infections and the complications that may arise as a result of them. These treatments aim to prevent infections by significantly increasing low serum IgG levels.[10] Rarely, IGRT can be used in a group of patients, such as patients with Hyper IgE syndromes, who have antibodies that are numerically normal but functionally defective. It is known that the serum IgG levels in primary immunodeficiency patients with antibody deficiency are closely related to the frequency and severity of respiratory tract infections. For this reason, higher serum IgG levels are targeted in patients with bronchiectasis or with a high tendency to develop bronchiectasis. Standard IVIG-RT consists of monthly infusions with a maintenance dose of 400-600 mg/kg.[11] Subcutaneous immunoglobulin, on the other hand, is administered weekly or bi-weekly with a maintenance dose of 100 mg/kg.[12] As a result, the amount of monthly dose is similar in both types of replacement therapy. The trough level of IgG is utilized as a monitoring indicator for infection prevention[9], SCIG-RT has been shown to result in lower IgG peaks and higher IgG troughs.[9] A total IgG dose divided into 3 or 4 equal weekly or

**Table 2. Compare of serum IgG levels, frequency of infections and frequency of lower respiratory tract infections by Wilcoxon signed-rank test**

| | | | | |
|---|---|---|---|---|
| **Compare of serum IgG levels** | IVIG-RT (median: 810 mg/dl) | SCIG-RT at first 6 months (median: 1020 mg/dl) | SCIG-RT at second 6 months (median: 1035 mg/dl) | SCIG-RT at second year (median: 1014 mg/dl) |
| Before IVIG-RT (median: 590 g/dl) | p=0.001* | p=0.000* | p=0.000* | p=0.000* |
| **Compare of frequency of infections** | IVIG-RT (median:3/year) | SCIG-RT at first year (median:2/year) | SCIG-RT at second year (median: 1/year) | |
| Before IVIG-RT (median:8/year) | p=0.002* | p=0.001* | p=0.000* | |
| **Compare of serum IgG levels** | SCIG-RT at first 6 months (median: 1020 mg/dl) | SCIG-RT at second 6 months (median: 1035 mg/dl) | SCIG-RT at second year (median: 1014 mg/dl) | |
| IVIG-RT (median: 810 mg/dl) | p=0.000* | p=0.003* | p=0.002* | |
| **Compare of frequency of infections** | SCIG-RT at first year (median:2/year) | SCIG-RT at second year (median: 1/year) | | |
| IVIG-RT (median:3/year) | p=0.004* | p=0.000* | | |
| **Compare of frequency of lower respiratory tract infections** | SCIG-RT at first year (median: 0/year) | SCIG-RT at second year (median: 0/year) | | |
| IVIG-RT (median:0/year) | p=0.157 | p=0.84 | | |

*p<0,05

bi-weekly portions should result in less variation and fluctuation in the IgG trough level. Thus, SCIG-RT provides a more stable trough level. The serum IgG level, which rises rapidly in IVIG-RT, may drop to low levels before the next replacement process, and even withdrawal symptoms such as fatigue and susceptibility to infections can be observed in patients during this period.[13] Withdrawal symptoms are not observed in SCIG-RT. In our study, the frequency of infections was statistically significantly decreased in each period of immunoglobulin replacement therapy compared to the pre-treatment period. The frequency of infections was lower during the SCIG-RT application period when the frequency of infections during IVIG-RT was compared to the first and second years of SCIG-RT. However, this study did not find a significant difference in lower respiratory tract infections was not determined between the IVIG-RT and SCIG-RT periods. The infection rate analysis in many studies similar to ours has shown that the annual infection rate with SCIG-RT is very low and there are no serious bacterial infections.[14,15]

Similarly, in a meta-regression comparing SCIG-RT with IVIG-RT, higher trough levels were found to be associated with lower infection rates with SCIG.[9] However, IVIG therapy did not show such a relationship.[9] While an increase in serum IgG levels would normally be expected after the initiation of immunoglobulin RT, the data obtained in this study showed that the mean serum IgG levels of SCIG-RT were significantly higher than the mean levels while taking IVIG. In this comparison, the serum IgG levels in all three periods of SCIG-RT treatment, namely the first 6 months, the second 6 months, and the second year were also significantly higher than the mean levels while receiving IVIG. Similar to our study, an adult study found that SCIG was more effective than IVIG in increasing serum Ig levels (mean IVIG=8.54 g/L and mean SCIG=9.59 g/L).[16] Similarly, in a comparative study of SCIG-RT versus IVIG-RT in pediatric patients, SCIG treatment resulted in significantly higher serum IgG trough levels at 16, 24, and 36 weeks when compared to previous IVIG treatment.[17] Our study also included patients with hyper-IgE syndrome and ataxia

telangiectasia who were receiving immunoglobulin replacement therapy. The immunoglobulin levels in these patients with known dysfunctional immunoglobulins were not low. Accordingly, the mean immunoglobulin-G levels prior to IGRT were not found to be extremely low. Although in some cases serum IgG levels were normal or high before replacement therapy, the increase in mean serum IgG levels after replacement was found to be significant in the overall group. Although there is no clear consensus on the target serum IgG levels in IGRT patients, it is recommended that the serum IgG concentration be greater than 500mg/dl.[18,19] Additionally, recommendations are given to support the notion that for effective infection management, target levels should be ≥800 mg/dl.[20] When monitoring the effectiveness of IGRT treatment, it is thought that it would be more appropriate to determine the level that provides the best infection control in the foreground on an individual basis, instead of aiming for a certain serum IgG level.[21] However, there is evidence that each 100 mg/dl increase in trough serum IgG levels results in a significant decrease in the incidence of pneumonia[12], emphasizing the importance of this level in infection control. While this study was limited to demonstrating a decrease in pneumonia incidence, we advocate that higher trough levels are also beneficial for overall infection prevention. The fact that SCIG-RT can achieve higher and more stable serum IgG levels, consistent with the data from our study, makes SCIG-RT more advantageous for infection control.

The primary strength of this study is that SCIG-RT clearly demonstrated higher IgG trough levels when compared to IVIG-RT. The effect of SCIG-RT on infection and pneumonia control can be supported by new studies with a larger patient group. Additionally, this study can be made more thorough by evaluating the impact of facilitated subcutaneous immunoglobulin replacement (fSCIG), which has become more popular in recent years, on IgG levels and infection prevention.

## CONCLUSION

Since both have advantages and disadvantages when deciding how to provide immunoglobulin replacement therapy, it is advised to collaborate with the patient to choose the most suitable approach. In addition, SCIG-RT appears to be a more advantageous option in terms of ease of use at home, decreased hospital admissions, and decreased potential adverse effects. Besides these, it enables stable and higher blood IgG levels, which provide sufficient defense against infections.

### Ethical approval

This study has been approved by the SBU İzmir Dr. Behcet Uz Education and Research Hospital Clinical Research Ethics Committee (approval date 22.12.2022, number 2022/22-10).

### Author contribution

Surgical and Medical Practices: SÖB, NG, FG; Concept: SÖB, NG, FG; Design: SÖB, NG, FG; Data Collection or Processing: SÖB, ÖA, İT, İAH, MŞK, FÇÇ, ÖS, CK, NG, FG; Analysis or Interpretation: SÖB, NG, FG; Literature Search: SÖB, ÖA, İT, İAH, MŞK, FÇÇ, ÖS, CK, NG, FG; Writing: SÖB, FG. All authors reviewed the results and approved the final version of the article.

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### Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

# Parenting knowledge of child development in Turkish mothers and fathers

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## ABSTRACT

**Objective:** Many studies have shown a positive relationship between parenting knowledge and early childhood development. We aimed to assess parenting knowledge about early childhood development and child-rearing in a sample of Turkish mothers and fathers.

**Methods:** A total of 106 married Turkish couples with children under the age of three participated in our study. Mothers and fathers completed 45 questions of the Knowledge of Infant Development Inventory (KIDI) and a sociodemographic questionnaire, individually. The KIDI is widely used in the international literature on child development and parenting knowledge. Permission to use the inventory was obtained from its author.

**Results:** The median KIDI questionnaire scores were 8 (min-max: (-10)- 20) for mothers and 6 (min-max: (-14)- 20) for fathers (maximum score 30). The average knowledge score obtained by mothers was significantly higher than the average score obtained by fathers (p=0.024). Maternal education is associated with parenting knowledge (p<0.001). Mothers had the most experience in changing diapers and dressing their children, while fathers had the most experience in playing with their children. The least experience for mothers and fathers was reading books with their children. It was found that mothers learned the information about their children mostly by talking to their families and fathers learned mostly by talking to their wives.

**Conclusion:** The results of the study show that Turkish couples' parenting knowledge, especially in child development, is an area that needs to be reinforced. Education level played an important role in parenting. Policies to improve parental education may also include increasing parental knowledge of child development.

**Keywords:** Child development, early childhood, knowledge of infant development inventory, parental knowledge, parenting

## INTRODUCTION

Brain plasticity and neurogenesis are at their highest level in early childhood. All of the neural networks that are formed and strengthened in children's developing brains are strongly influenced by their interactions and experiences with their environment in early childhood.[1,2] For these reasons, the first years of life are considered a "window of opportunity".[3] Early experiences of a child, both before and after birth, gain meaning according to the nature of the care environment and contribute to the neural interactions necessary for further neural restructuring.[3] The developmental support provided to

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the child during this period directly affects brain development by changing the genetic, biological, and psychosocial effects and helps to form a basis for positive developmental outcomes in children.[4,5]

Children's health and well-being depend on the ability of families and community support systems to promote positive emotional and physical development.[6] The fact that parents have the most significant and lasting influence in their children's lives and in supporting their development shows the importance of the strong influence of the cognitive and social support provided by them in the first years of life on child development.[7,8] Studies in Turkey and in low and middle-income countries (LMICs) show that interventions aimed at improving mother-child interactions and increasing developmentally facilitating activities have benefits on attachment, cognitive, social, emotional, and behavioral development when performed through home visits and/or individual parent counseling given in health centers.[9] Studies on fathers show that the time they spend with their children has increased approximately 3.5 times compared to previous years, and they have unique roles that may differ from mothers in child's health, especially in nutrition, exercise, play, and parenting behaviors (e.g., reading, discipline).[10]

Current parenting research increasingly focuses on knowledge of child development and educational practices.[11] It is seen that the developmental knowledge, attitudes, and practices of the parents play an essential role in establishing a quality and supportive relationship with the child.[12] Bornstein defines developmental knowledge as parents' knowledge of child development and how to meet the biological, physical, social, and emotional needs of a developing child. Several studies have been conducted in many countries, mostly in developed countries, examining parents' developmental knowledge and the effects of this knowledge on child development.[13-15] Many studies have shown a positive relationship between parenting knowledge of child development and early childhood development.[16,17] It has been shown that parents with better knowledge have more realistic expectations for themselves and their children and are more likely to treat their children in developmentally appropriate ways.[18] It is known that when parents have information about child development, they interact with their child in a more supportive way and ensure that the child's social and cognitive development is better. Parents who have a better understanding of the developmental stages of early childhood are better able to understand and meet their children's needs. They are also better at identifying developmental delays, unlike mothers or fathers who have less knowledge about child development.[19] In the case of a child with a developmental delay, it is known that parents usually notice the signs of delay first. Therefore, it is crucial for parents to observe their children's language, cognitive, motor, and emotional behaviors, have sufficient developmental knowledge, be aware of developmental delays, and provide appropriate stimuli and support in early childhood.[20]

Until recently, research on parenting has focused almost exclusively on mothers. This focus reflects the fact that, traditionally and across cultures, mothers assume the primary responsibility for early childhood care and much more involved in parenting activities than fathers.[21] However, research focus on fathers has increased significantly over the past two decades.[22] This study evaluates the developmental knowledge of parents of children aged 1-36 months who applied to the general pediatric outpatient clinic. In addition, it aims to present the relationship between the factors affecting parenting knowledge and investigate whether there are differences between parents in terms of developmental knowledge, their experiences with their children, and the ways in which parents can obtain information. There are almost no studies in Turkey that deal with the developmental knowledge of both mothers and fathers. We think that including fathers in the study and raising their awareness about child development will contribute to the literature.

## MATERIALS AND METHODS

### Type, Population, and Sample of the Study

The universe of this descriptive and prospective study consisted of parents (total number of participants: 212) of children aged 1-36 months, who applied to the University Faculty of Medicine, between March and May 2019. Mothers and fathers were invited to participate in the study from among all applications to the pediatric outpatient clinic, based on voluntary participation, and both parents from each family were included in the study. Children with known chronic diseases such as neurodevelopmental, genetic, or metabolic disease and premature births were excluded from the study. Families who did not speak Turkish at a sufficient level to continue the interview were not included in the study. Twenty-six out of 132 parents who were admitted to the clinic during the specified period refused to take part in the study. There was no sociodemographic difference between parents who accepted the study and those who did not ($p>.09$).

Approval was obtained from the university ethics committee on the date of 02.04.2019 with the issue number 2019/7-15.

### Data collection

The data were collected by the researchers using the questionnaire technique. Before data collection, the research was explained to the parents. Informed consent was obtained from all parents enrolled in the study. Mothers and fathers were asked to fill in the questionnaire separately. Families also filled out a comprehensive sociodemographic questionnaire. The surveys took a maximum of 30 minutes to complete. Couples with more than one child were asked to answer questions considering their 1 to 36-month-old child.

### Evaluation tools

The survey consists of 2 parts. In the first part, there are questions about socio-demographic characteristics. In the second part, there are forty-five questions taken from the "Child Development Information Form-KIDI" (The Knowledge of Infant Development Inventory). Permission to use and adapt the inventory was obtained from MacPhee. Twelve of the questions are about child development and health care, and eighteen of the questions are about what children can do according to their age. For the first twelve questions, parents were asked to check one of the options "agree," "disagree," or "not sure," and for the eighteen questions, they were asked to check "agree," "can do when young," "can do when older," or "not sure," depending on the age of their children. In the first 30 questions, there are subscale of norms (n=6), principles (n=7), and milestones (n=13). Seven questions asked parents to describe their experiences with their child as "never", "sometimes", "fairly often", and "regularly". The last eight questions are about where and how much they learned about their experiences and knowledge about children. Participants were asked to describe how much they preferred each way of obtaining information by choosing one of the options "very little", "some but not much", "a fair amount" and "a lot".

KIDI was translated into Turkish from English. The questionnaire was translated back into English by another person. The back translation was compared with the original English version. The Cronbach alpha coefficient for 45 questions in the questionnaire was calculated to be 0.709.

### KIDI (Knowledge of Infant Development Inventory)

The Knowledge of Infant Development Inventory was first developed by MacPhee in the USA in 1981 and revised in 2002. KIDI is a 58-item self-report tool designed to assess information about parenting, child development processes, and child behavior standard deviation. The KIDI is widely used in the international literature examining child development and parenting knowledge.[14,23]

The Cronbach α value as a result of the reliability analysis for the internal consistency of the KIDI tool is found to be 0.82. Considering the test-retest reliability results, the internal consistency was found to be 0.92. Because the KIDI is a knowledge assessment tool, it has precise answers, and therefore answers are marked as correct (1 point) or incorrect (lost 1 point). If the answer to a question is "I am not sure.", the participant does not receive any points for that item. The KIDI scores are reported as a percentage of questions answered correctly, with a higher rate indicating greater knowledge of child development.

### Data analysis

The conformity of quantitative variables to normal distribution was checked with Kolmogorov-Smirnov and Shapiro-Wilk tests. Quantitative variables that provided the assumption of normal distribution were summarized as mean and standard deviation and quantitative variables that did not show normal distribution were summarized as median and min-max. Mann-Whitney U test, Kruskal-Wallis test, and Conover's test for pairwise comparisons were used for the variables that did not show normal distribution in the statistical analysis. Independent samples t-test was used for normally distributed variables. Spearman Rho correlation coefficient analysis was performed for correlation analysis. Qualitative variables were summarized with frequency (percent), and Yates corrected chi-square and Pearson chi-square tests were used. In this study, in addition to baseline comparisons, effect sizes were calculated to evaluate the effect of each parameter on mothers and fathers. Effect size is defined as the difference between groups.[24] The general interpretation of the effect size in the literature is that values between 0.01-0.06 indicate a small effect, values between 0.06-0.14 indicate a medium effect, and values above 0.14 indicate a significant effect.[25] $p<0.05$ was considered statistically significant. Python 3.9 Version and SPSS 25.0 programming languages were used for data analysis.[26,27]

## RESULTS

Two hundred and twelve patients, 106 (50%) mothers, and 106 (50%) fathers, with a mean age of 29.85 ± 5.82 for mothers and 33.49 ± 5.86 for fathers, were included in the study. Descriptive statistics and effect sizes of the mother and father groups according to the sociodemographic variables of the data set are given in Table 1. When Table 1 is examined, there is a statistically significant difference between the mothers and fathers participating in the study in terms of age and work

**Table 1. Participant characteristics**

| Variable | | Parent Groups | | | | | | Effect Size | p value |
|---|---|---|---|---|---|---|---|---|---|
| | | Mother | | | Father | | | | |
| | | Mean ± SD | n | % | Mean ± SD | n | % | | |
| Age | | 29.85 ± 5.82 | - | - | 33.49 ± 5.86 | - | - | 0.623 | **0.0001*** |
| Year of Education | 8 years and below | - | 40 | 37.7 | - | 30 | 28.3 | 0.129 | 0.17** |
| | 9-12 Years | - | 29 | 27.4 | - | 41 | 38.7 | | |
| | 13 Years and above | - | 37 | 34.9 | - | 35 | 33.0 | | |
| Working status | Yes | - | 23 | 21.7 | - | 97 | 91.5 | 0.704 | **0.0001**** |
| | No | - | 83 | 78.3 | - | 9 | 8.5 | | |
| | | Sociodemographic Data on the Child | | | | | | | |
| | | Mean ± SD | | n | | % | | | |
| Child age as month | | 16.35 ± 9.66 | | - | | - | | | |
| Gender of child | Girl | - | - | 61 | | 57.5 | | - | - |
| | Boy | - | - | 45 | | 42.5 | | | |
| Number of child | 1 | - | - | 50 | | 47.2 | | | |
| | 2 and above | - | - | 56 | | 52.8 | | | |

SD: Standard deviation; *: Independent Samples t Test; **: Chi-Square test; Bold values denote statistical significance at the p<0.05 level.

status variables. The effect size for the working situation is (0.704); it shows that the difference between mothers and fathers in terms of work status is quite significant. In other words, the working rate of mothers participating in the study is relatively low compared to that of fathers.

In our study, 56.9% of the mothers and 53.3% of the fathers gave correct answers to the first thirty questions. When Table 2 is examined, there is a statistically significant difference between the mothers and fathers participating in the study in terms of total scores. The total score of the mothers was higher than that of the fathers. The knowledge level of mothers is significantly higher than that of fathers. According to the effect size results for the total score, it is seen that this difference between mothers and fathers is a large clinical difference (effect size: 0.313). In addition, there was a statistically significant difference between the education level groups of mothers in terms of the total score. It was observed that the total score value increased as the mother's education level increased. This difference between the education level groups has a significant clinical impact (effect size: 0.391). The principle score was higher in mothers than in fathers (Table 2). There was a statistically significant and positive correlation between mothers and fathers in terms of the principle and milestone subscales (Table 3).

In the mother and father groups, a statistically significant relationship was found between the categories of "I learned by reading magazines or books about children", "I learned by talking to my family (mother, father, sister, grandmother)", and "I learned by talking to my wife". It was observed that mothers learned most information about their children by talking to their families (74.6% n=79). It was observed that fathers learned information about their children most by talking to their spouses (76.4% n=81) (Table 4).

A statistically significant relationship was found between the categories of giving a bath, changing diapers, dressing, taking charge of feeding playing together, putting him /her to bed, reading to him/her in the mother and father groups. In Table 5, there is a statistically significant relationship between mothers and fathers in terms of parents' experiences with their children. The most frequent (fairly often and regularly) experiences of mothers with their children were changing diapers and dressing. It was determined that the least common experience of mothers with their children was reading a book to their children. The most common experience fathers have with their children is playing with them. It has been determined that the least common experience fathers have with their children is reading a book and dressing their child. (Table 5).

**Table 2. Total scores of the participants**

| Variable | | Total Score | | | Effect size | p value |
|---|---|---|---|---|---|---|
| | | Median | Minimum | Maximum | | |
| Mother: 1 Father: 2 | Mother (Mother higher than father) | 8.00 | -10.00 | 20.00 | 0.313 | **0.024*** |
| | Father | 6.00 | -14.00 | 20.00 | | |
| Mother education level | 8 years and below | 5.5[b] | -10.00 | 16.00 | 0.391 | **0.0001**** |
| | 9-12 years | 6[b] | -4.00 | 14.00 | | |
| | 13 years and above | 11[a] | -5.00 | 20.00 | | |
| Father education level | 8 years and below | 5.00 | -14.00 | 11.00 | 0.251 | 0.112** |
| | 9-12 years | 7.00 | -4.00 | 20.00 | | |
| | 13 years and above | 7.00 | -4.00 | 20.00 | | |
| Gender of child | Girl | 6.00 | -14.00 | 20.00 | 0.166 | 0.228* |
| | Boy | 8.00 | -11.00 | 20.00 | | |
| Number of child | 1 | 7.00 | -9.00 | 20.00 | 0.201 | 0.14* |
| | 2 and above | 7.00 | -14.00 | 20.00 | | |
| Working status | Yes | 7.00 | -14.00 | 20.00 | 0.107 | 0.43* |
| | No | 6.00 | -9.00 | 20.00 | | |

*: Mann-Whitney U test; **: Kruskal Wallis-H; a, b: There is a statistically significant difference in group categories that do not contain the same letter; Bold values denote statistical significance at the p<0.05 level.

**Table 3. Correlation relationship of participants in terms of total score and subscales (mothers and fathers)**

| Variable | Statistics | Mothertotal score | Father total score | Mother norm subscale | Father norm subscale | Mother principles subscale | Father principles subscale | Mother milestone subscale | Father milestone subscale |
|---|---|---|---|---|---|---|---|---|---|
| Mother total score | Rho | 1 | 0.510 | 0.650 | 0.251 | 0.676 | 0.331 | 0.822 | 0.414 |
| | p-value | - | **0.0001** | **0.0001** | **0.01** | **0.0001** | **0.001** | **0.0001** | **0.0001** |
| Father total score | Rho | 0.510 | 1 | 0.481 | 0.461 | 0.299 | 0.696 | 0.376 | 0.746 |
| | p-value | **0.0001** | - | **0.0001** | **0.0001** | **0.002** | **0.0001** | **0.0001** | **0.0001** |
| Mother norm subscale | Rho | 0.650 | 0.481 | 1 | 0.374 | 0.343 | 0.384 | 0.317 | 0.264 |
| | p-value | **0.0001** | **0.0001** | - | **0.0001** | **0.0001** | **0.0001** | **0.001** | **0.006** |
| Father norm subscale | Rho | .251 | 0.461 | 0.374 | 1 | 0.133 | 0.243 | 0.119 | -0.015 |
| | p-value | **0.01** | **0.0001** | **0.0001** | - | 0.174 | **0.012** | 0.225 | 0.876 |
| Mother principles subscale | Rho | .676 | .299 | .343 | 0.133 | 1 | 0.241 | 0.298 | 0.273 |
| | p-value | **0.0001** | **0.002** | **0.0001** | 0.174 | - | **0.013** | **0.002** | **0.005** |
| Father principles subscale | Rho | 0.331 | 0.696 | 0.384 | 0.243 | 0.241 | 1 | 0.189 | 0.311 |
| | p value | **0.001** | **0.0001** | **0.0001** | **0.012** | **0.013** | - | 0.052 | **0.001** |
| Mother milestone subscale | Rho | 0.822 | 0.376 | 0.317 | 0.119 | 0.298 | 0.189 | 1 | 0.365 |
| | p value | **0.0001** | **0.0001** | **0.001** | 0.225 | **0.002** | 0.052 | - | **0.0001** |
| Father milestone subscale | Rho | 0.414 | 0.746 | 0.264 | -0.015 | 0.273 | 0.311 | 0.365 | 1 |
| | p value | **0.0001** | **0.0001** | **0.006** | 0.876 | **0.005** | **0.001** | **0.0001** | - |

Bold values denote statistical significance at the p<0.05 level.

**Table 4. Parents' ways of obtaining information**

| How much have you learned about infants from | | Mother | | Father | | Effect size | p-value |
|---|---|---|---|---|---|---|---|
| | | n | % | n | % | | |
| The mass media – radio, movies, television, or newspapers. | Very little | 39 | 36.8 | 49 | 46.2 | 0.113 | 0.43 |
| | Some but not much | 35 | 33.0 | 33 | 31.1 | | |
| | A fair amount | 23 | 21.7 | 19 | 17.9 | | |
| | A lot | 9 | 8.5 | 5 | 4.7 | | |
| Reading magazine articles or books about infants or toddlers. | Very little | 27[a] | 25.5 | 50[b] | 47.2 | 0.272 | **0.001** |
| | Some but not much | 31 | 29.2 | 33 | 31.1 | | |
| | A fair amount | 33[a] | 31.1 | 16[b] | 15.1 | | |
| | A lot | 15 | 14.2 | 7 | 6.6 | | |
| Watching infants and their parents when you were younger | Very little | 17 | 16.0 | 14 | 13.2 | 0.093 | 0.6 |
| | Some but not much | 22 | 20.8 | 23 | 21.7 | | |
| | A fair amount | 43 | 40.6 | 51 | 48.1 | | |
| | A lot | 24 | 22.6 | 18 | 17.0 | | |
| Talking to your own family (mother, father, sister, grandparent) | Very little | 12 | 11.3 | 17 | 16.0 | 0.193 | **0.048** |
| | Some but not much | 15 | 14.2 | 24 | 22.6 | | |
| | A fair amount | 57[a] | 53.8 | 37[b] | 34.9 | | |
| | A lot | 22 | 20.8 | 28 | 26.4 | | |
| Talking to friends of other adults who have babies of their own | Very little | 16 | 15.1 | 23 | 21.7 | 0.1 | 0.54 |
| | Some but not much | 44 | 41.5 | 44 | 41.5 | | |
| | A fair amount | 28 | 26.4 | 26 | 24.5 | | |
| | A lot | 18 | 17.0 | 13 | 12.3 | | |
| Comparing your baby or child to others whom you see or know | Very little | 50 | 47.2 | 46 | 43.4 | 0.07 | 0.78 |
| | Some but not much | 30 | 28.3 | 35 | 33.0 | | |
| | A fair amount | 19 | 17.9 | 16 | 15.1 | | |
| | A lot | 7 | 6.6 | 9 | 8.5 | | |
| Talking to doctors or nurses before and after your baby was born | Very little | 27 | 25.5 | 42 | 39.6 | 0.15 | 0.18 |
| | Some but not much | 34 | 32.1 | 27 | 25.5 | | |
| | A fair amount | 26 | 24.5 | 22 | 20.8 | | |
| | A lot | 19 | 17.9 | 15 | 14.2 | | |
| Talking to your husband (wife) | Very little | 29[a] | 27.4 | 9[b] | 8.5 | 0.323 | **0.0001** |
| | Some but not much | 25 | 23.6 | 16 | 15.1 | | |
| | A fair amount | 33 | 31.1 | 38 | 35.8 | | |
| | A lot | 19[a] | 17.9 | 43[b] | 40.6 | | |

a, b: There is a statistically significant difference in group categories that do not contain the same letter; Bold values denote statistical significance at the p<0.05 level.

**Table 5. Parents' experiences with their babies and children**

| Variable | | Mother | | Father | | Effect size | p-value |
|---|---|---|---|---|---|---|---|
| | | n | % | n | % | | |
| Give baths | Never | 3 | 2.8 | 18 | 17.0 | 0.56 | **0.0001** |
| | Sometime | 3 | 2.8 | 43 | 40.6 | | |
| | Fairly Often | 30 | 28.3 | 15 | 14.2 | | |
| | Regularly | 70 | 66.0 | 30 | 28.3 | | |
| Change diapers | Never | 1 | 0.9 | 38 | 35.8 | 0.767 | **0.0001** |
| | Sometime | 3 | 2.8 | 46 | 43.4 | | |
| | Fairly Often | 34 | 32.1 | 9 | 8.5 | | |
| | Regularly | 68 | 64.2 | 13 | 12.3 | | |
| Dress him or her | Never | 1 | 0.9 | 11 | 10.4 | 0.685 | **0.0001** |
| | Sometime | 3 | 2.8 | 58 | 54.7 | | |
| | Fairly Often | 35 | 33.0 | 26 | 24.5 | | |
| | Regularly | 67 | 63.2 | 11 | 10.4 | | |
| Take charge of feeding | Never | 1 | 0.9 | 10 | 9.4 | 0.607 | **0.0001** |
| | Sometime | 6 | 5.7 | 56 | 52.8 | | |
| | Fairly Often | 29 | 27.4 | 21 | 19.8 | | |
| | Regularly | 70 | 66.0 | 19 | 17.9 | | |
| Play with him or her | Never | 3 | 2.8 | 5 | 4.7 | 0.256 | **0.0003** |
| | Sometime | 27 | 25.5 | 31 | 29.2 | | |
| | Fairly Often | 33 | 31.1 | 51 | 48.1 | | |
| | Regularly | 43 | 40.6 | 19 | 17.9 | | |
| Put him or her to bed | Never | 5 | 4.7 | 13 | 12.3 | 0.406 | **0.0001** |
| | Sometime | 13 | 12.3 | 39 | 36.8 | | |
| | Fairly Often | 26 | 24.5 | 31 | 29.2 | | |
| | Regularly | 62 | 58.5 | 23 | 21.7 | | |
| Read or sing to him or her | Never | 21 | 19.8 | 36 | 34.0 | 0.197 | **0.042** |
| | Sometime | 51 | 48.1 | 51 | 48.1 | | |
| | Fairly Often | 15 | 14.2 | 8 | 7.5 | | |
| | Regularly | 19 | 17.9 | 11 | 10.4 | | |

Bold values denote statistical significance at the p<0.05 level.

**Table 6. The relationship between the education level and the number of children**

| Parent | Variable | | Education level | | | p-value* |
|---|---|---|---|---|---|---|
| | | | 8 years and below | 9-12 years | 13 years and above | |
| | | | n (%) | n (%) | n (%) | |
| Mother | Number of child | 1 | 14 (35.00) | 13 (44.83) | 23 (62.16) | 0.109 |
| | | 2 and above | 26 (65.00) | 16 (55.17) | 14 (37.84) | |
| Father | Number of child | 1 | 14 (46.70) | 18 (43.90) | 18 (51.40) | 0.805 |
| | | 2 and above | 16 (53.30) | 23 (56.10) | 17 (48.60) | |

*Chi-Square test

Chi-square analysis was performed to examine the relationships between the number of children and the education level of the parents, and there was no significant relationship between the education level and the number of children (Table 6).

## DISCUSSION

There are few studies in the literature on child development in Turkey, but this is the first study in Turkey to examine both parents' knowledge of child development.[13,28] Parents' knowledge of child development, health and safety, and parenting is important in many ways. Because parents are the primary caregivers of young children, the extent and quality of parenting information is often considered vital to improving children's development and health.[11] Increased paternal knowledge facilitates higher levels of mutuality in couples where men are also a resource for their wives, thereby increasing their self-efficacy and reducing the partner's burden of responsibility.[29] Parenting knowledge is also relevant, particularly in pediatric practice.[30] During child health visits, clinicians and other health professionals ask parents about their observations and their views, expectations, and concerns about their children's health and development. Therefore, accurate and complete developmental history and surveillance depend heavily on the knowledge base of parents. Parents, who have the most experience with their children, are believed to know their child best and are the clinician's primary external source of information about their child's development.[11] If parents have inaccurate information that a developmental skill emerges later or earlier than it should, they will either be worried that their child is not performing the skill they expected, or they will not realize if they are delayed in performing the skill. In this case, they may not provide their children with enough stimulation to help them develop these skills. Another consequence of this situation is a missed opportunity to detect developmental delays. Inadequate parental awareness of developmental stages may delay the identification and intervention of developmental delays. The quality of clinical assessments and the effectiveness of clinical recommendations can be considerably improved by incorporating parental inputs.

The existing data available on parental information are mostly about mothers. Few studies have examined fathers' knowledge of parenting specifically.[21,29] In the study conducted by Scarzello et al.[29] in Italy with 157 couples (n: 314) who were the parents of children aged 16 to 36 months, mothers gave an average of 65% correct answers to the KIDI questions, and fathers gave 63% correct answers. In our study, mothers answered 56.9% of the questions correctly, and fathers answered 53.3% correctly.

In the study by Scarzello et al.[29], it was found that parents scored lower on the norms and milestones subscales, and the total score for knowledge about child development was relatively low. Similarly, in our study, low scores were obtained from the norms and milestone subscales, the lowest score was obtained in the milestone subscale.

In the study of Bornstein in 2005 with 70 Brazilian parent couples, the average KIDI score received by the mothers was significantly higher than the average score received by the fathers. It was determined that the scores of couples raising boys were not different from the scores of couples raising girls. Education was found to be correlated with parenting knowledge, and the educational attainments of parents were found to be correlated with each other. The age of parents was not associated with KIDI scores for mothers and fathers separately and together. The age of children was associated with the mother's KIDI scores, but not with fathers' KIDI scores. More educated parents, mothers, and parents with older children showed more parenting knowledge. Mothers' education was found to be significantly associated with parenting knowledge. Only fathers with higher levels of education had more parenting knowledge. A significant difference was found between the total scores of KIDI knowledge between mothers and fathers. [21] There was also a statistically significant difference between the scores of mothers and fathers in the principle subscale. The principle subscale score was higher in mothers than in fathers. This is also consistent with our study.

In a study conducted in Brazil, 64 primiparous mothers of 5-month-old infants living in Rio de Janeiro were administered the Brazilian version of KIDI. No difference in parenting knowledge was found between mothers of boys and mothers of girls. Mothers' education was found to be the best indicator of parenting knowledge. This study supported the view that educational attainment, an important indicator of socioeconomic status, plays a key role in parental knowledge.[31] Parental knowledge about children's access to developmental milestones and skills varies significantly between cultural groups and is influenced by parental education. It is important for health professionals to be aware of these differences in order to correctly interpret parents' reports of a child' health, development, and behavior. Overall, the results suggest that one of the best strategies for improving parenting knowledge is to enhance parental education. In our study, we see that as the education level of the mother increases, the level of knowledge about child development increases. This difference between education level groups has a large clinical impact (effect size: 0.391). However, our study could not detect a significant relationship between the father's education level and the level of knowledge about child development.

It is interesting to note that maternal knowledge was not related to birth order. Multiparous mothers were no more knowledgeable than primiparous mothers. It is generally assumed that adult mothers with older children require less support and information than first-time mothers. These data show us that previous experience does not necessarily increase mothers' knowledge about parenting.[32] Such a relationship was not found in our study either.

Traditionally, mothers take primary responsibility for early childcare and are more involved in childcare activities than fathers. Dessen and Braz confirmed that in the example of Brazilian families with low social support and low socioeconomic status, Brazilian mothers take the primary responsibility for household and childcare activities, even though fathers support mothers.[33] In many cultures, infancy is considered a passive period in which little learning takes place; as a result, parental roles are limited to feeding and bathing.[34,35] Zellman et al.[36] study of Moroccan parents with children aged six and under revealed a strong view that parental responsibilities in the early years of a child are focused on feeding, dressing, and keeping the child safe and clean. Our study revealed that mothers' most common experiences with their children were changing their diapers and dressing them, and fathers' most common experience was playing games with their children. The literature often describes differences in the way parents interact with their children and suggests that spend more time playing with their children rather than providing care.[37,38]

In the study of Scarzello et al.[29], when analyzing the sources of information that mothers and fathers refer to obtain information about development, it was found that the most important source for mothers was friends and family. The most important source of information for fathers was their spouses, followed by family and friends. The least used source of information for both parents was the mass media. The study showed that parents used multiple sources of information based on direct and indirect experiences presented in the socio-cultural context, including family, friends, and expert sources. By identifying their partners as the primary source of information, fathers showed that they were aware of the information gap between themselves and their partners. Mothers refer more often to their families and friends and do not consider their spouses to be a reliable source of information about their children. It is also true that "new fathers" often think that mothers mediate their role, even though they are more involved in children's lives from birth.[39] In our study, it was seen that mothers learned the most information about their children by talking to their families, and fathers learned the most by talking to their spouses.

### Limitations

The limitation of the study is that it was single-centered and cross-sectional. If this study were conducted in a multi-center population, the results would be representative of the whole country. In addition, the sample size was affected by the fact that it covered childhood in a certain age group. The inclusion of fathers and the use of an internationally validated assessment tool are the strengths of the study.

## CONCLUSIONS

First of all, the data in our study show us weak areas of parental information that need reinforcement. Parents have insufficient knowledge about norms and milestones, which are quite significant for guidance in structuring a suitable environment for the child and providing activities according to their ages. In order to diagnose children with developmental risks and delays as early as possible and to provide appropriate support, it is essential to understand the level of developmental knowledge of their families. In addition, determining the level of developmental knowledge of caregivers is a critical issue, considering the potential benefits of early diagnosis and developmental support. Policies to improve parental education may also include increasing parental knowledge of child development.

### Ethical approval

This study has been approved by the İnönü University Health Sciences Non-Invasive Clinical Research Ethics Committee (approval date 02.04.2019, number 2019/7-15). Written informed consent was obtained from the participants.

### Author contribution

Surgical and Medical Practices: ŞGB, FNA, YDÖ; Concept: ŞGB, DGD, SK, FNA, YDÖ; Design: ŞGB, DGD, SK, FNA, YDÖ; Data Collection or Processing: ŞGB, FNA, YDÖ; Analysis or Interpretation: ŞGB, DGD, FHY; Literature Search: ŞGB, DGD, SK, FNA, YDÖ; Writing: ŞGB, DGD, SK. All authors reviewed the results and approved the final version of the article.

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### Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

# Trust, distrust and skepticism: Parent's perspective on COVID-19 prevention and vaccination in children aged 0-5 years

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## ABSTRACT

**Objective:** The study aimed to determine the attitudes of parents with children aged 0-5 years towards protecting their children from COVID-19, the rate of those who hesitated to have their children vaccinated, and the factors causing hesitation.

**Methods:** In this descriptive, cross-sectional study, we conducted a survey with parents of children aged 0-5 years from July 2021 to May 2022.

**Results:** Four hundred and sixty-four parents with children 0-5 years of age were analyzed. The mean age of the participants was 34.6 ± 7.3 years and the mean number of children was 1.79 ± 0.78, the majority (72%) of which were mothers. The main source of information for COVID-19 was television channels for the participants (68.5%). Parents most often chose to wash their hands (91%) to prevent their children from contracting COVID-19. Fifty-seven percent of parents, especially those whose source of information for COVID-19 was social media platforms (OR 1.45 [1-2.1], p= 0.048), distrusted the measures they took to prevent their children from contracting COVID-19. Fifty-one percent of parents distrusted hospital measures to prevent transmission of COVID-19, and 55% were hesitant to get their children vaccinated for COVID-19. Increasing parental age (OR 1.02 [1.01-1.05], p= 0.040), having a family member who has had COVID-19 (OR 1.47 [1.01-2.16], p= 0.043), and parents' trust in hospital COVID-19 measures (OR 2.04 [1.41-2.91], p= 0.001) have increased the desire to vaccinate their children against COVID-19.

**Conclusion:** Considering that vaccination is the most important step in preventing infection, information provided to parents by reliable authorities can help increase vaccination acceptance rates.

**Keywords:** Attitude, child, COVID-19, parents, vaccination

## INTRODUCTION

The coronavirus-2019 (COVID-19) pandemic has become the largest modern public health emergency with 661 million infections diagnosed worldwide as of December 2022.[1] Since the SARS-CoV-2 virus, which is the causative agent of the disease, is highly contagious, children of all ages can be affected, and its incidence in children is similar to that in adults. Their role in the spread of the disease cannot be ignored, as children can transmit COVID-19, whether they are symptomatic or not.[2-5] Inevitably, interventions were needed both to contain the pandemic and to help parents protect their children from COVID-19.[6-9] Although personal protective behaviors are very important in controlling the pandemic, vaccination is the most important step.[10,11] Considering that the American Academy of Pediatrics recommends vaccination of all children aged 6 months and older with no contraindications, it can be predicted that the COVID-19 vaccination in children will now become the

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new 'routine'.[12,13] However, the emergences of new variants as well as the hesitation of vaccination are among the obstacles to control the disease.[4] As with other vaccine-preventable diseases, vaccine hesitancy, which means delaying or refusing vaccination despite the availability of vaccines, has gained importance within the scope of COVID-19 vaccination in children as a result of medical mistrust.[2,4,11,14,15] However, the success of the vaccination program depends on the public's desire to be vaccinated. Because parents decide on behalf of their children, their attitudes toward vaccination play a vital role in their willingness to vaccinate their children.[4,14,16] Unfortunately, COVID-19 is not the first virus to threaten humanity, and it may not be the last. Therefore, given the strong correlation between trust in healthcare providers and the medical system and vaccine acceptance, it is crucial to fully understand parents' attitudes in order to establish an ecosystem of trust.[9,15,17,18] In our study, we primarily focused on determining the attitudes of parents with children aged 0-5 years to protect their children from COVID-19 infection, the rate of those who hesitated to vaccinate their children, and the factors causing the hesitation.

## MATERIALS AND METHODS

### Study design

In this descriptive, cross-sectional study, we conducted a survey of parents of children aged 0-5 years from July 2021 to May 2022.

### Target population, study sample and data collection

The target population was the parents of children aged 0-5 years who were followed up in the Pediatrics Clinic of Çanakkale Onsekiz Mart University Hospital, who could read and understand Turkish. We conducted the research at a time when COVID-19 vaccines were not yet approved for children in this age group. In the literature review on vaccine hesitancy in the community, it was reported that 65.4% of parents with children aged 0-5 years were hesitant to have their children vaccinated against COVID-19.[19] The sample size was calculated using the formula $n=Z\alpha^2 P (1-P) / d^2$. In the formula, $Z\alpha=1.96$ for the 95% confidence interval and the estimated acceptable margin of error d=0.05, and the minimum sample size was calculated as 386 parents. However, we collected a larger sample to better represent the target population.

### Study procedure

The protocol and informed consent of the study were approved by the Clinical Research Ethics Committee of Çanakkale Onsekiz Mart University [date: 09.06.2021, no: 2021-06]. Before participating in the study, members of the research team experienced in conducting surveys asked each parent if they could participate in the study after introducing themselves. Interested participants were informed of the identity of the researcher, the purpose/importance of the research, the fact that participation is voluntary, the survey will not contain the personal information of the participants, the duration of the survey, how the data will be stored, they can stop filling out the survey whenever they want, and the information will be used for scientific research purposes. Written informed consent was obtained from those who agreed to participate in the study. Participants were not offered any incentives for their time.

### Survey instrument

Within the scope of the research, a survey developed based on the literature was used to determine the attitudes of the parents.[10,11,19] In addition to the questions in Table 1, the form included the parent's gender, age, number of children, residence (rural/urban), level of education (secondary education or lower/ Bachelor's degree or higher), COVID-19 information sources (Table 2), history of COVID-19 infection, and personal precautions taken to prevent the transmission of COVID-19 to their child. The self-administered questionnaire consisted of 17 questions that could be completed in 5 minutes.

### Outcome measures

The primary outcome was parents' attitudes toward protecting their children from COVID-19, the secondary outcome was the proportion of those who hesitated to vaccinate their children with COVID-19 vaccines, and the tertiary outcome was to identify risk factors for vaccine hesitancy.

### Data analysis

The Statistical Package for the Social Sciences program (SPSS, version 23.0, IBM Company) was used for statistical analysis of the data. Descriptive statistics such as mean ± standard deviation (SD), frequency (n), and percentage (%) were used to generate summary tables for study variables. Univariate binary logistic regression analysis was performed to determine the relationship between participants' socio-demographic characteristics and sources of information, and their trust in protective measures and their intention to have their children vaccinated against COVID-19. A p value of $< 0.05$ was used to determine the statistical significance.

| Table 1. Parents' responses to survey questions | | |
|---|---|---|
| **Questions** | **Answers (numbers of parents, [percentage]) N=464** | |
| Are you worried about your child contracting COVID-19? | Yes | No |
| | 428 (92) | 36 (8) |
| How well do you follow physical distancing rules? | Always | Sometimes/never |
| | 352 (76) | 112 (24) |
| Do you think children are transmitting the COVID-19 infection? | Yes | No/not sure |
| | 294 (63) | 170 (37) |
| Do you trust the measures you take to prevent the transmission of COVID-19? | Yes | No/not sure |
| | 201 (43) | 263 (57) |
| If your child had a fever and/or cough, would you take them to the hospital immediately? | Yes | No/not sure |
| | 341 (73) | 123 (27) |
| Do you think hospitals are more dangerous than other public places? | Yes | No/not sure |
| | 289 (62) | 128 (28) |
| Can doctors transmit COVID-19 to your child during the examination? | Yes | No/not sure |
| | 177 (38) | 287 (62) |
| Do you trust the measures taken in the hospital to prevent the transmission of COVID-19? | Yes | No/not sure |
| | 229 (49) | 235 (51) |
| Would you to vaccinate your child for COVID-19? | Yes | No/not sure |
| | 210 (45) | 254 (55) |

## RESULTS

### Parents characteristics and source of COVID-19 information

Of 526 participants with children 0-5 years old, 464 (88.2%) were analyzed (Figure 1). The mean age of the participants was 34.6±7.3 years, and the mean number of children was 1.79±0.78. The majority (72%) were mothers, those living in the city (87.9%), those with secondary education or lower (69%). The sources of information for COVID-19 were mostly television channels, social media platforms, and the website of the Ministry of Health. The socio-demographic characteristics and information sources of the parents are presented in Table 2.

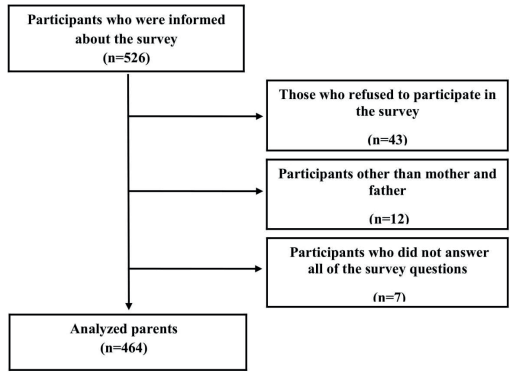


**Figure 1.** Flowchart of participant selection

### Parents' attitudes and trust in protecting their children from COVID-19

Ninety-two percent of the parents were concerned about their child being infected with COVID-19. Washing hands (91%), ventilating the room (80%), and wearing masks (74%) were the most frequently preferred practices of parents to prevent their children from contracting COVID-19, and not sending them to daycare and leaving them in the house were also among the preferred practices (Table 3). Fifty-seven percent of parents, especially parents whose source of information for COVID-19 was family members/friends (OR 1.9 [1.27-2.84], p= 0.002) or social media platforms (OR 1.45 [1-2.1], p= 0.048), distrusted the measures they took to prevent their children from contracting COVID-19. Fifty-one of the parents did not trust the measures

**Table 2. Parent characteristics and source of COVID-19 information**

| Characteristic | Numbers of parents (Percentage) N=464 |
|---|---|
| Parent, Mother | 335 (72.2) |
| Parent age, years (mean ±SD) | 34.6±7.3 |
| Number of children (mean ±SD) | 1.79±0.7 |
| Urban residents | 408 (87.9) |
| Secondary education or lower | 320 (69) |
| Presence of a family history of COVID-19 infection | 178 (38.4) |
| COVID-19 information | |
| Television channels | 318 (68.5) |
| Social media platforms | 262 (56.5) |
| Ministry of health website | 241 (51.9) |
| Google etc. | 169 (36.4) |
| Family/Friends | 157 (33.8) |
| Scientific articles | 104 (22.4) |
| Newspapers | 64 (13.8) |
| I am not interested | 8 (1.7) |

**Table 3. Practices of parents to protect children from COVID-19 infection**

| Practices | Numbers of parents (Percentage) N=464 |
|---|---|
| I make my child wash their hands often | 423 (91) |
| I often ventilate my child's room | 371 (80) |
| I wear a mask when my child goes out | 345 (74) |
| I often disinfect his/her hands with cologne/alcohol | 329 (71) |
| I change my child's mask every day | 316 (68) |
| I only feed my child cooked food | 203 (44) |
| I allow my child to consume peelable fruit | 182 (39) |
| I clean the packaged food and give it to my child | 181 (39) |
| I do not accept guests | 101(22) |
| I do not take my child to crowded places | 78 (17) |
| I do not send my child to daycare | 39 (8) |
| I do not take my child out of the house | 31 (7) |

taken in the hospital to prevent COVID-19 transmission. Thirty-eight percent of the parents, especially parents who have only one child (OR 2.13 [1.45-3.13], p= 0.048), thought that doctors could infect their children with COVID-19 during the examination (Table 1).

**Parents' willingness to vaccinate their children against COVID-19**

Fifty-five percent of parents were hesitant about getting their children vaccinated for COVID-19 (Table 3). Parental gender, level of education, place of residence, number of children, and source of information for COVID-19 did not change willingness to vaccinate, but the desire to vaccinate their children increased slightly as parent age increased (OR 1.02 [1.01-1.05], p= 0.040). Having a family history of COVID-19 infection increased the willingness of parents to vaccinate their children (OR 1.47 [1.01-2.16], p= 0.043). In addition, trust in hospital measures to prevent transmission of COVID-19 was another factor that increased parents' willingness to vaccinate their children (OR 2.04 [1.41-2.91], p= 0.001) (Table 4).

## DISCUSSION

This study, which we conducted with the participation of 464 parents at a time when COVID-19 vaccines were not yet approved for children aged 0-5 years, has two main findings. Firstly, 57% of parents distrusted the measures they took to prevent their children from contracting COVID-19, 51% distrusted the measures taken in the hospital, and 38% thought doctors could transmit COVID-19 to their children during the examination. Secondly, 55% of parents were hesitant about getting their children vaccinated against COVID-19. Risk factors for vaccine hesitancy were found as lack of trust in the measures taken to prevent COVID-19 transmission in the hospital, young age of parents, and no family history of COVID-19 infection.

Studies evaluating the effectiveness of personal protective behaviors during the COVID-19 pandemic shows that behaviors such as mask use, maintaining physical distance and washing hands can prevent transmission.[10,11] As in our study, it is known that the majority of parents take precautions such as using masks, washing hands and avoiding crowded environments because they are worried about their children being infected with COVID-19.[6,20-22] However, despite all these precautions, parents may think that they cannot adequately protect their children from COVID-19.[9] People tend to carry out preconceived ideas even when information is easily accessible.[23] In addition, distrust of healthcare providers and the medical system in today's society has been exacerbated by the inconsistencies in scientific communication during the COVID-19 era.[23,24]

| Table 4. Factors affecting parents' decision to vaccinate their 0-5 year old children with COVID-19 | | |
|---|---|---|
| **Factors** | **OR (95% CI)*** | **p-value**** |
| Parent | | |
| Mother | Reference | |
| Father | 1.12 (0.71-1.64) | 0.586 |
| Parent age | 1.02 (1.01-1.05) | **0.040** |
| Number of children | 1.08 (0.85-1.36) | 0.515 |
| Family history of COVID-19 infection | | |
| Yes | 1.47 (1.01-2.16) | **0.043** |
| No | Reference | |
| I trust personal protective measures | | |
| Yes | 0.84 (0.50-1.05) | 0.071 |
| No/Not sure | Reference | |
| I trust the protective measures in the hospital | | |
| Yes | 2.04 (1.41-2.91) | **0.001** |
| No/Not sure | Reference | |

*OR (95% CI): Estimated relative risk and 95% confidence interval represented by odds ratio
** Boldface used to indicate statistical significance, where p-value <0.05

Since COVID-19 was an "infodemia" of both true and false information at the same time.[25] Therefore, it is inevitable that parents are skeptical about the effectiveness of the protective measures taken. However, trust in science is even more important in times of social change and distress.[26] Medical distrust, defined as "the tendency to distrust medical systems and personnel believed to represent the dominant culture in a given society", is associated with less acceptance of medical advice.[24] In our study, although the majority of parents took personal protective measures to protect their children from COVID-19, about half did not rely on these measures. For this reason, we think that the Ministry of Health and reliable scientists should inform parents about the effectiveness of protective measures and the safety of health services, especially through social media platforms.

Vaccination is a fundamental measure and an inalienable right to protect public health.[14,27] Vaccination of children against COVID-19 is also important as it can reduce the spread by providing herd immunity as well as preventing the disease.[20,28,29] It is reported that 38-87% of parents with ≤5 children have a positive opinion about having their children vaccinated against COVID-19, and some have concerns about this issue.[19-21,30,31] In general, factors that influence vaccine acceptance are trust (trust in vaccine efficacy and safety), indifference (perception of disease risk), evaluation (weighing up risks and benefits of vaccines), and restraint (availability of information about vaccines).[20] Particularly, the rapid development of COVID-19 vaccines has raised concerns that the vaccine may be 'experimental', and/or that its side effects may not have been adequately investigated.[21,32,33] Studies have shown that the lack of a reliable source of information about COVID-19 vaccines and concerns about their safety and efficacy in young children are associated with parents' reluctance to have their children vaccinated against COVID-19.[13,28] Similar to our study, Sabra et al.[20] demonstrated that the majority of parents are hesitant to get vaccinated against COVID-19, even though they are worried about their child getting COVID-19 and perceive it as a serious illness. Therefore, we think that the main reason why parents do not want to have their children vaccinated against COVID-19 may be concerns about the safety of COVID-19 vaccines in children. However, as we have shown in our study, while low trust in healthcare personnel contributes negatively to this process, trust in healthcare, science and scientists contributes positively to vaccination.[15,25,26,31,34-36] The effect of trust in science on attitudes towards vaccination indicates that the message conveyed must be scientifically reliable and understandable.[34] Studies show that most parents require information about the COVID-19 vaccine, and providing sufficient information to hesitant parents increases their likelihood of vaccinating their children.[4,37] However, given that doctors are the most preferred source of information for parents to vaccinate their children[38], and that hesitant parents trust their pediatricians the most[18], we think that pediatricians, in particular, should provide parents with comprehensive and objective information about the efficacy and safety of COVID-19

vaccination in children. The findings should be interpreted in light of some potential methodological limitations inherent in our study. Firstly, as in most surveys, parents may have given socially desirable responses rather than reflecting their actual behaviors, so interpreting the relationships described can be difficult. Secondly, since the survey was conducted in a region of Turkey, it may not reflect the situation across the country. Thirdly, because data on vaccines continue to be published, parents may have different perspectives than when our survey was conducted.

## CONCLUSION

This study gives a brief idea of what parents need to vaccinate their 0-5 year old child against COVID-19. Especially considering that vaccination will be the most important step in preventing infection and nearly half of the parents are hesitant about vaccination, informing parents by reliable authorities, especially pediatricians, can help increasing vaccination acceptance rates. In addition, national studies are needed to investigate the causes of medical distrust in the safety of not only vaccination against COVID-19, but also future vaccination campaigns.

### Ethical approval

This study has been approved by the Çanakkale Onsekiz Mart University Clinical Research Ethics Committee (approval date 09.06.2021, number 2021-06). Written informed consent was obtained from the participants.

### Author contribution

Surgical and Medical Practices: TÇ, BBT; Concept: TÇ, BBT; Design: TÇ, BBT; Data Collection or Processing: TÇ, BBT; Analysis or Interpretation: TÇ, BBT; Literature Search: TÇ, BBT; Writing: TÇ, BBT. All authors reviewed the results and approved the final version of the article.

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### Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

# Pediatric brucellosis in the central mediterranean region of Türkiye: Insights from a single-center experience

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## ABSTRACT

**Objective:** We aimed to contribute to the literature by presenting the epidemiologic, clinical, and laboratory characteristics of pediatric patients with brucellosis followed up by our clinic.

**Method:** The medical records of patients aged 0-18 years who were followed up with a diagnosis of brucellosis in Gazi University Pediatric Infectious Diseases Clinic between 2010-2020 were retrospectively analyzed. The effect of demographic, clinical, and laboratory markers on diagnosis was investigated.

**Results:** The mean age was 162.0 ± 55.5 months. Of the 47 patients included in our study, 68% lived in rural areas. While 82.5% had a background of consuming raw milk and dairy products, 55% had experience in animal husbandry. Twenty-two patients had a family history of brucellosis. The most common symptoms were joint pain in 85%, malaise in 78%, and muscle pain in 42%. The most common associated findings were fever in 59%, joint stiffness in 23%, and splenomegaly in 17%. The decrease in erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) values and the increases in leukocytes, hemoglobin, and platelets before and after treatment were statistically significant ($p<0.001$). Anemia was the most common in the patients, followed by neutropenia, thrombocytopenia, thrombocytosis, leukocytosis, and pancytopenia, respectively. Blood culture positivity was 12%. Of 47 patients with positive tube agglutination titer, Rose Bengal was positive in 80% and negative in 19%.

**Conclusion:** Brucellosis remains an important public health problem in Türkiye. Patients should be questioned in detail in the presence of fever, arthralgia, hepatosplenomegaly, and pancytopenia which presents with different clinical findings. Rose Bengal negativity, which is used as a screening test, should not mislead us in making a diagnosis in the presence of clinical suspicion. Tube agglutination tests should definitely be performed in patients with suspected brucellosis. In addition, changes in non-specific blood parameters such as CRP, ESR, leukocytes, hemoglobin, and platelets may be indicative for clinicians.

**Keywords:** Blood, brucellosis, childhood

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## INTRODUCTION

Brucellosis is one of the most common zoonotic bacterial infections worldwide.[1] Brucellosis is endemic in the Mediterranean basin including Turkey, the Middle East, Central Asia, China, the Indian subcontinent, sub-Saharan Africa and Mexico, and parts of Central and South America. Worldwide, approximately 500,000 cases are reported annually.[2] According to the Turkish Ministry of Health reports, 9,818 cases were reported in 2008 and this number was last updated to 6,457 cases in 2017 (morbidity rate 7.99 per 100,000).[3]

Brucellosis, which is an important public health problem in Türkiye, is transmitted to humans mainly through the consumption of unpasteurized dairy products or contact with tissues of infected animals (cattle, sheep, goats, pigs) or inhalation of infected aerosolized droplets.[4-6]

The causative Brucella species are small gram-negative coco-bacilli. While six species can cause disease in animals, only four species (*B. abortus, B. melitensis, B. suis* and, less commonly, *B. canis*) cause disease in humans.[3,5,6] Brucellosis is a systemic disease that can be very difficult to diagnose in children. Symptoms may be acute or insidious and are usually non-specific. Brucellosis typically presents with fever, malaise, night sweats, and joint pains.[2,5] Physical examination findings are variable but non-specific; hepatomegaly, splenomegaly, and/or lymphadenopathy may be seen. Laboratory findings of brucellosis may include elevated transaminases and hematologic abnormalities, including anemia, leukopenia, or leukocytosis with relative lymphocytosis, and thrombocytopenia.[2,6] Additionally, in endemic countries, Brucella spp. may be an important cause of occult bacteremia in children.[6]

Due to the insufficient number of reports and diagnostic difficulties, there are not many series of childhood brucellosis in the literature and there are few publications on this subject in Türkiye.[7,8]

In this study, we aimed to contribute to the literature by presenting the epidemiologic, clinical, and laboratory characteristics of pediatric patients with brucellosis followed up in our clinic.

## MATERIALS AND METHODS

In this study, a patient group consisting of 51 pediatric patients aged 0-18 years who were followed up with a diagnosis of brucellosis in Gazi University Pediatric Infectious Diseases Clinic between January 1, 2010 and January 1, 2020 were accepted as the population and their files were retrospectively reviewed. Patients with a history of underlying comorbidity, organ involvement, complications, and incomplete medical records were excluded from the study. Patients' age, gender, risk factors for brucellosis (consumption of unpasteurized milk/dairy products, living in a rural area, and being engaged in animal husbandry), and family history of similar diseases were recorded. Patients were asked whether they had received treatment in an external center before they were referred to us. Admission complaints and physical examination findings, laboratory (complete blood count, liver function tests, C-reactive protein (CRP) and erythrocyte sedimentation rates (ESR), and microbiological tests were evaluated. Liver function tests, CRP, ESR, leukocyte, platelet, and hemoglobin values in the complete blood count were evaluated according to the age-specific normal values. In addition, the patients in our study were compared with regard to the laboratory parameters examined one day before the treatment and after the treatment. Blood cultures were performed using automated BACTEC (Becton Dickinson Diagnostic Instruments, Sparks, MD) and samples were kept for at least two weeks. The diagnosis of brucellosis was confirmed by a positive blood culture and/or a positive slide agglutination/STA (>1:160) test. SPSS version 25.0 (IBM Corp., Armonk, New York, USA) statistical software was used for data analysis. Categorical variables are presented as numbers and percentages, and numerical variables are presented as mean ± standard deviation and median. The compatibility of the numerical variables with normal distribution was tested with the Kolmogorov-Smirnov test and the Mann-Whitney U test was used to evaluate the non-normally distributed data. The statistical significance level was accepted as $p<0.05$. This study was approved by Gazi University Clinical Research Ethics Committee on 09/01/2023.

## RESULTS

Of the 47 patients included in the study, 41 (87.2%) were male, 6 (12.8%) were female and the mean age was 162.0 ± 55.5 months. Of the 47 patients with brucellosis, 32 (68%) lived in rural areas and 26 (55%) had a history of animal husbandry. In our study, 27 (82.5%) patients had a history of consuming raw milk and dairy products and 22 (46%) patients had a history of active brucellosis in their relatives. Twenty-seven of these patients had received irregular treatment in external centers before being referred to us.

Joint pain (85%), malaise (78%), and myalgia (42%) were the most common symptoms, while fever (59%), limitation of movement in the joint (23%), and splenomegaly (17%) were the most common associated findings (Table 1).

| Table 1. Clinical Characteristics of Pediatric Patients Diagnosed with Brucella | |
|---|---|
| **Symptoms (n= 47)** | |
| Arthralgia (+), n (%) | 40 (85.1) |
| Malaise (+), n (%) | 37 (78.7) |
| Myalgia (+), n (%) | 20 (42.6) |
| Night sweats (+), n (%) | 19 (40.4) |
| Weight loss (+), n (%) | 18 (38.3) |
| Headache (+), n (%) | 16 (34.0) |
| Abdominal pain (+), n (%) | 15 (31.9) |
| Vomiting (+), n (%) | 14 (29.8) |
| Skin rash (+), n (%) | 11 (23.4) |
| **Findings (n= 47)** | |
| Fever ≥38 ° C (+), n (%) | 28 (59.6) |
| Limitation of joint movement (+), n (%) | 11 (23.4) |
| Splenomegaly (+), n (%) | 8 (17.0) |
| Lymphadenopathy (+), n (%) | 6 (12.8) |
| Increase in joint temperature (+), n (%) | 4 (8.5) |
| Joint swelling (+), n (%) | 3 (6.4) |
| Hepatomegaly (+), n (%) | 2 (4.3) |

Anemia was the most common in the patients, followed by neutropenia, thrombocytopenia, thrombocytosis, leukocytosis, and pancytopenia, respectively (Table 2).

While the decrease in ESR and CRP values after treatment was statistically significant ($p<0.001$), a statistically significant increase was also found in leukocyte, hemoglobin (Hb), and platelet (plt) values after treatment ($p<0.001$). The change in liver transaminase levels was not statistically significant ($p>0.05$) (Table 3).

Blood culture positivity was found in 6 (12%) cases. While the Rose Bengal screening test was positive in 38 (80%) of 47 cases with a positive brucella tube agglutination titer, it was remarkable that the test was negative in 9 (19%) cases.

## DISCUSSION

Brucellosis is a bacterial zoonotic infection that has not yet been eradicated worldwide and is observed at a higher rate, especially in the Eastern and Southeastern Anatolia regions in Türkiye.[2,3] Every year, 500 thousand new cases of brucellosis occur in the world, and the incidence rate in Türkiye range between 1% and 26.7% depending on the geographical region.[2,9]

| Table 2. Laboratory Characteristics of Pediatric Patients Diagnosed with Brucella at the Time of Diagnosis | |
|---|---|
| Anemia, n (%) | 8 (17.0) |
| Leukocytosis, n (%) | 2 (4.3) |
| Leukopenia, n (%) | 8 (17.0) |
| Thrombocytopenia, n (%) | 4 (8.5) |
| Thrombocytosis, n (%) | 3 (6.9) |
| Pancytopenia, n (%) | 1 (2.1) |
| Increased ESR, n (%) | 15 (31.9) |
| Increased CRP, n (%) | 21 (44.7) |
| Increased transaminase, n (%) | 9 (19.1) |

Although pediatric brucellosis is seen in all ages and sexes in Türkiye, in case series written on this subject, it is more common in the male sex and the mean age is reported to be between 5-11 years.[7,10] The mean age and gender results obtained in our study were found to be compatible with the literature.

In countries where the disease is endemic, such as Türkiye, the main mode of transmission is the consumption of raw milk and dairy products, while in developed countries, transmission by inhalation or direct contact with an infected animal is more prominent.[2,5,6]

Studies conducted in Türkiye have reported a history of consumption of raw milk and dairy products ranging between 21% and 80%.[10,11] In our study, a significant proportion of participants reported a history of consuming raw milk and dairy products. In a study of adult cases from Türkiye, the rate of animal contact was 44%, while this rate was 55.3% in our study.[12] This may be due to the fact that 68.1% of the cases lived in rural areas.

Since the most common mode of transmission is through the consumption of infected food, more than one case of brucellosis may be found in the same family. It is therefore very important to perform a family screening to evaluate other family members for symptoms and findings when brucellosis is diagnosed. In our study, about half of the patients had a family history of brucellosis, and this rate is supported by similar results in other pediatric studies.[13]

In brucellosis, the presence of very different symptoms and signs, which are non-specific and can be confused with many other diseases, may lead to delays in diagnosis and treatment.[2] In our study, the most common symptom was joint pain, followed by fatigue, muscle pain, and night sweats. The most common findings were fever, limitation of movement in the

| Table 3. Comparison of Laboratory Characteristics of Pediatric Patients with Brucella at Diagnosis and After Treatment | | | |
|---|---|---|---|
| **Laboratory Features** | **At Diagnosis** | **After Treatment** | **p value** |
| **Leukocyte** (x$10^3$ /$mm^3$ ) (n=47) Mean ± SD | 6.23 ± 1.55 | 6.86 ± 1.98 | **p<0.001** |
| Median | 5.80 | 6.43 | |
| Range (min- max ) | 4.10 – 12.30 | 4.00 – 13.94 | |
| **Platelets** (x$10^3$ /$mm^3$ ) (n=47) Mean ± SD | 2.61 ± 0.59 | 2.67 ± 0.66 | **p<0.001** |
| Median | 2.56 | 2.83 | |
| Range (min- max ) | 1.45 – 3.89 | 1.24 – 4.00 | |
| **Hemoglobin** (%) (n=47) Mean ± SD | 12.58 ± 1.01 | 12.88 ± 1.60 | **p<0.001** |
| Median | 12.80 | 13.20 | |
| Range (min- max) | 9.5 – 14.2 | 9.7 – 14.7 | |
| **ESH** (mm/h) (n= 47) Mean ± SD | 23.11 ± 18.80 | 10.47 ± 6.76 | **p<0.001** |
| Median | 6.43 | 10.00 | |
| Range (min- max) | 2 – 84 | 2 – 26 | |
| **CRP** (mg/L) (n= 47) Mean ± SD | 27.28 ± 31.01 | 5.40 ± 4.57 | **p<0.001** |
| Median | 13.30 | 4.51 | |
| Range (min- max) | 1 – 125 | 1 – 25 | |
| **ALT** (U/L) (n= 47) Mean ± SD | 46.02 ± 41.40 | 26.66 ± 19.91 | p=0.498 |
| Median | 27 | 20 | |
| Range (min- max) | 6 – 180 | 6 – 90 | |
| **AST** (U/L) (n= 47) Mean ± SD | 45.17 ± 30.70 | 28.45 ± 10.06 | p=0.210 |
| Median | 34 | 28 | |
| Range (min- max) | 14 – 169 | 10 – 52 | |
| **Culture growth** (+) (n= 47) | 6 (12%) | | |

joint, splenomegaly, and lymphadenopathy. The symptoms and findings in our study were similar to those reported in the case series related to this subject in the literature.[14-16]

Although hematologic involvement is frequently observed in brucellosis, it is not diagnostic and usually does not require treatment.[2,17] Hematologic disorders including anemia, leukopenia, thrombocytopenia, and pancytopenia can be observed in childhood brucellosis.[2,6,16] In our study, the most commonly observed hematologic disorders were anemia and leukopenia (17%).

Thrombocytopenia was found in 8.5%, thrombocytosis in 6.9%, and pancytopenia in 2.1%. Our findings were similar to those in other studies on this subject.

Acute phase reactants are supportive rather than diagnostic in brucellosis cases. They may be high or normal.[2,6,17] In our study, a considerable number of participants had elevated levels of ESR, while a significant portion had increased levels of CRP. In our study, the decrease in ESR and CRP values before and after treatment was statistically significant (p<0.001).

This is associated with the expected decrease in inflammatory markers following the treatment. The increase in leukocyte, hemoglobin (Hb), and platelet (plt) values after treatment was statistically significant (p<0.001) (Table 3).

The liver is often affected by brucellosis. Liver enzymes generally tend to increase in this disease. Some studies reported transaminase elevation in 18.3-55%.[7,14,18] In our study, transaminase elevation was found in approximately one-fifth of the patients. These findings were compatible with the literature. In addition, no significant statistical change was found in liver transaminase levels with treatment in our study (p>0.05).

Brucellosis is diagnosed on the basis of positive serological tests and/or the production of the agent in culture.[2,5,6] Serologic

tests are very important for diagnosis. For this purpose, the tube agglutination test (Wright), slide agglutination test (Rose Bengal), complement-fixation test, and ELISA are used.[2,5,6] The most commonly used test in Türkiye is the Wright test.[14,15] Although a single titer is not diagnostic, it is found to be 1/160 and above in most patients with active infection.[2,6,17] In our patients, antibody titers ranged between 1/160 and 1/320. In a study on Rose Bengal agglutination test, which is one of the serologic tests with a short turnaround time used for screening purposes Türkiye, sensitivity and specificity were found to be 87% and 100%, respectively.[2] In our study, the fact that the Wright agglutination test result was positive in nine patients with a negative Rose Bengal test revealed the importance of performing further investigation in cases of clinical suspicion.

The definitive diagnosis in patients with brucellosis is made by producing the causative agent.[2,17] In various studies reported outside our country, the growth rate of the causative agent in blood culture in children with brucellosis varied between 23.5% and 57%.[19,20] In a study reported from our country, the rate of growth in blood culture was reported to be 72%.[15] In our study, the growth rate in blood culture was found to be 12%. This growth rate was lower than in previous studies, which we interpreted as being related to the inadequate and irregular drug use history of the patients before they presented to our center.

Our study had some limitations. Since our study was a single-center study, the number of cases was small, making it difficult to attribute the data to the general population. In addition, the fact that it was a retrospective study and that the data were collected by scanning the medical records and computer database was another limiting factor. Not all data were accessible due to technical problems in the database. Prospective and multicenter studies on the subject are important and necessary to provide up-to-date clinical and surveillance data.

## CONCLUSION

Brucella can clinically mimic many diseases and may present with various non-specific signs and symptoms. This is directly related to delays in diagnosis and treatment. In Türkiye, it is important to take a family history in terms of brucellosis and to ask about suspicious food consumption for early diagnosis in patients presenting with fever, hepatosplenomegaly, bicytopenia, or elevated transaminases. In cases with brucellosis, it is usually not possible to produce the causative agent in culture, and Rose Bengal test negativity, which is used as a screening test, should not mislead us in making a diagnosis in the presence of clinical suspicion. In addition to serologic tests, changes in non-specific blood parameters such as CRP, ESR, leukocytes, hemoglobin, and platelets may guide clinicians in treatment follow-up.

### Ethical approval

This study has been approved by the Gazi University Clinical Research Ethics Committee (approval date 09.01.2023, number 11). Informed consent was not required because of the retrospective design.

### Author contribution

Surgical and Medical Practices: EG, TBD, EYO, SHA, VM, NAÜ; Concept: EG, TBD, EYO, NKU, HT, AT; Design: EG, TBD, EYO, SHA, VM, NKU, HT, AT; Data Collection or Processing: EG, TBD, EYO, SHA, NKU, HT, AT; Analysis or Interpretation: EG, TBD, VM; Literature Search: EG, TBD, EYO, SHA, VM, NAÜ; Writing: EG. All authors reviewed the results and approved the final version of the article.

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### Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

# Characteristics of Klebsiella bloodstream infections and risk factors for carbapenem-resistant Klebsiella infections in children

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## ABSTRACT

**Objective:** *Klebsiella spp.* is a common and severe pathogen of bloodstream infections (BSI) due to gram-negative bacilli. Carbapenems are commonly used agents for the treatment of serious infections. However, the incidence of carbapenem-resistant (CR) *Klebsiella* infections has increased significantly in recent years. The aim of this study was to determine the characteristics, risk factors, and outcomes of BSI caused by *Klebsiella spp.* in a tertiary care pediatric hospital.

**Method:** A retrospective review of pediatric patients with BSI caused by *Klebsiella spp*. between August 2019 and September 2021 was conducted. Patients with CR isolates were compared with carbapenem-susceptible (CS) isolates for risk factors, outcome, and mortality.

**Results:** Among 345 *Klebsiella* isolates, 95 (27.5%) were CR. Catheter-related bloodstream infections (CRBSI) accounted for 52.4% of infections. There was an underlying disease in all patients, most commonly malignancy (31.3%). Mechanical ventilation, percutaneous endoscopic gastrostomy (PEG) tube feeding, previous antibiotic use, especially carbapenems, aminoglycosides, glycopeptides, fluoroquinolones, and colistin, ($p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$, $p:0.033$, $p<0.001$, respectively) were strongly affected the development of BSI due to CR *Klebsiella spp.* Antibiotic treatment in the previous 14 days increased the risk of developing carbapenem resistance by 14 times. Elevated C-reactive protein (CRP) ($p<0.001$), thrombocytopenia ($p<0.001$), CRBSI ($p=0.002$), use of indwelling devices, previous antibiotic therapy (carbapenems, aminoglycosides, glycopeptides, colistin) ($p=0.002$), and carbapenem resistance ($p=0.001$) increased the risk of mortality from *Klebsiella*-associated BSI. The use of colistin in treatment was higher in the CR group ($p<0.001$). The 28-day mortality was 15.7%.

**Conclusion:** CR *Klebsiella spp.* Infections are important and serious causes of BSI in children. The use of indwelling devices and previous antibiotic therapy are risk factors for mortality and carbapenem resistance. Preventive measures, including targeted antimicrobial therapy, good surveillance networks, and less invasive procedures, are important aspects of infection control management in children.

**Keywords:** Antibiotic resistance, carbapenem, children, *Klebsiella*

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## INTRODUCTION

Gram-negative infections are major problems due to the lack of treatment options, long hospital stays, high morbidity and mortality, and lack of sufficient clinical data, especially in children. *Klebsiella spp.* is the most common cause of infections due to gram-negative bacilli and has been increasing over the years.[1] Analysis of 2003 data from the United States National Nosocomial Infection Surveillance System showed that 23.8% of bacteraemias were due to gram-negative bacteria, and K. pneumoniae accounted for 4.2% of all bacteraemias and 18% of gram-negative bacteraemias. In the data of Brazilian Surveillance and Control of Pathogens of Epidemiological Importance, between 2007 and 2011, the BSI due to gram-negative bacteria was 58.5%, and *Klebsiella spp.* (12%) was the most common gram-negative bacteria.[1,2] The prevalence of CR gram-negative bacteria has increased significantly in recent years, largely due to the emerging new resistance mechanisms resulting from the widespread use of antimicrobial agents.[3] Resistance to carbapenems leaves very limited treatment options, especially for children, and makes antimicrobial resistance a global threat today.[4,5]

*Klebsiella spp*. (mostly *K. pneumoniae*) is a serious opportunistic pathogen, causing urinary tract infections, pneumonia, and localized infections (such as liver abscess) as well as BSI.[6,7] Approximately 75% of the BSIs are healthcare-related.[8-10]

CR *Klebsiella* infections, which have been on the rise in recent years, pose a particular problem in pediatric patients due to their high mortality and the fact that there are fewer treatment options than in adults. More data are needed to understand the predictability of those infections, determine the epidemiologic profile, and guide our empiric treatment options. Therefore, we designed this study to evaluate the demographic and clinical characteristics, treatment, and response to treatment of patients with BSI caused by *Klebsiella spp*. and to determine the risk factors of patients with and without carbapenem resistance.

## MATERIAL AND METHODS

In our study, blood cultures sent between August 2019 and September 2021 in Ankara Bilkent City Hospital with a capacity of 610 beds were retrospectively analyzed. The results of blood cultures and catheter cultures taken from children aged 1 month to 18 years in the pediatric intensive care unit, pediatric surgery service and intensive care, pediatric burn unit, bone marrow transplant unit, palliative intensive care, and pediatric services of our hospital were scanned from the registration systems.

### Study group

Blood cultures and catheter cultures, *Klebsiella spp.* (*K. pneumoniae, K. oxytoca*) culture results, culture antibiograms, and patient records were analyzed using the registration systems. Demographic characteristics (age, gender), hospital inpatient service, underlying disease, mechanical ventilation, presence of a central venous catheter, presence of a urinary catheter, PEG tube feeding, treatment received, presence of neutropenic fever, antimicrobial exposure (only the ones for at least 48 h during the previous 14 days were: carbapenems, fluoroquinolones, glycopeptides, cephalosporins, aminoglycosides, colistin, β-lactam- β- lactamase inhibitor combinations and exposure to combined antimicrobials) were studied. Duration of treatment, time to culture negativity, type of infection (BSI, CRBSI), mortality in the last 28 days, leukocyte count, neutrophil count, lymphocyte count, platelet count, CRP, and culture antibiogram result were recorded. If there were multiple episodes of *Klebsiella* infection in a patient, only the first one was included in the risk factor analysis. Polymicrobial culture results were not included in the study. Patients who started treatment but died before the end of the culture-negative period were excluded.

### Definitions

Nosocomial infections were defined according to the surveillance diagnostic criteria determined by the Centers for Diseases Control and Prevention (CDC) in the United States (USA).[4]

A laboratory-confirmed BSI is defined as a) a pathogen identified by culture or non-culture microbiological testing of the patient's blood specimen for clinical diagnosis or treatment, and b) the organisms identified in the blood are not associated with a localized infection at another site.[4,11]

For a definitive diagnosis of CRBSI, the same organism must be isolated from at least one peripheral blood culture and one catheter tip culture, or two simultaneous positive blood cultures from the catheter hub and peripheral vein must meet CRBSI criteria.[12,13]

CR *Klebsiella* was performed according to the definition of CR Enterobacterales by the CDC. According to this, at least one CR (specifically, minimum inhibitory concentrations of ≥4 mcg/ml for doripenem, imipenem, meropenem, or ≥2 mcg/ml for ertapenem) or by the production of a carbapenemase should be considered as CR *Klebsiella*.[3,10] In our study, the definition was made according to the antibiogram results.

### Microbiological methods

Samples were inoculated on routine 5% Sheep Blood agar and MacConkey agar. After 16-24 hours of incubation at 37°C, the growing isolates were identified using VITEK® MS (bioMérieux, France). Antimicrobial susceptibility profiles of the isolates of *K.pneumoniae and K.oxytoca* were determined using VITEK® 2 Compact (bioMérieux Vitek, Hazelwood, MO, ABD), and interpreted according to the Clinical and Laboratory Standards Institute's criteria for other non-Enterobacteriaceae. Antibiotic susceptibility tests were performed in accordance with the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines for Enterobacterales.[14]

### Statistical analysis

All statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS) version 22.0 (SPSS Inc). The data of the patients were collected retrospectively from the hospital records. The distribution of the data was tested using the Kolmogorov–Smirnov test. Categorical variables were presented as numbers and percentages. Continuous data were presented as medians (IQR). The medians of parameters were compared using the Mann–Whitney U test. The Chi-square test was used in the comparison of categorical variables between independent groups. Multivariate logistic regression analysis was used to determine the effect of risk factors on carbapenem resistance and mortality. The results of the regression analysis were expressed as odds ratio (OR) and 95% confidence interval. A value of p<.05 was considered statistically significant.

## RESULTS

A total of 345 pediatric patients, including 250 (72.5%) CS *Klebsiella spp.* and 95 (27.5%) CR *Klebsiella spp.* in BSI were included in the study. CRBSI accounted for 52.4% of the infections. An underlying disease was present in all patients, most commonly malignancy (31.3%). There was immunodeficiency in 38% of the patients, 108 (31.3%) were patients with malignancy and 24 (6.9%) had immunosuppressed conditions. One hundred and twenty patients (34.7%) had febrile neutropenia. The median age of the CS group was 17 months and the median age of the CR group was 19,5 months. Most of the patients in the CS and CR groups were male 56,4% and 54,7%, respectively. Mechanical ventilation (p<0.001) and PEG tube feeding (p<0.001) were significantly higher in the CR group. Table 1 shows the comparison of demographic, clinical characteristics, underlying diseases, and risk factors of patients with CS and CR groups. In the present study, the association of antibiotic use prior to the diagnosis of BSI was analyzed. About half of the patients (170/345) had used antibiotics in the last 14 days. Previous use of combination antibiotics (p<0.001), carbapenems (p<0.001), aminoglycosides (p<0.001), glycopeptides (p<0.001), fluoroquinolones (p=0.033), and colistin (p<0.001) was higher in CR isolates compared to CS isolates, previous use of cephalosporins was higher in CS isolates (p=0.03) (Table 1).

Thrombocytopenia was more common and the median thrombocyte count was statistically significantly lower in the CR group (p=0.04). The median CRP level was 85 mg/L and CRP values were higher in the CR group (p<0.001) (Table 2).

The duration of treatment for infection (14 days [IQR, 1 - 40]) (p=0.03) and the time to culture negativity with treatment (3 days) (p=0.002) were statistically longer in the CR group (Table 2). Most of the *Klebsiella spp.* were *K. pneumoniae* (326/345), while most of the *K. oxytoca* were CS (17/19) (Table 2). In the CR group, meropenem or β-lactam β-lactamase inhibitor combination therapy was given prolonged infusion according to the minimum inhibitory concentration (MIC) value of the culture antibiogram.

Table 3 shows the multivariate logistic regression analysis testing the relationship between clinical variables and carbapenem resistance. In the multivariate logistic regression analysis, thrombocyte counts (OR, 0.997: 95% CI, 0.995–1; p=0.037), PEG tube feeding (OR, 29.332: 95% CI, 8.715–98.726; p<0.001), antibiotic use in the last 14 days (OR, 14.096: 95% CI, 3.45–57.597; p<0.001) were found to be the independent predictors of CR. Antibiotic treatment in the last 14 days increased the risk of developing carbapenem resistance by 14 times (Table 3).

The 28-day mortality rate was 15.7%. The comparison of the demographic, clinical characteristics, and laboratory findings of the patients with the mortality group (MG) was shown in Table 4. While the lymphocyte and platelet counts were statistically significantly lower in the MG group (p=0.016 and p<0.001), the CRP value was found to be higher in the MG (p<0.001). Mortality was higher in patients with CR (p=0.001). CRBSI had a higher mortality rate than BSI (72.2%) (p=0.002). The presence of a central venous catheter, mechanical ventilation, PEG tube feeding, and urinary catheter was statistically significantly higher in the MG (p=0.006, p<0.001, p:011 and p<0.001, respectively). In terms of antibiotics used in the treatment, it was observed that the use of amikacin and cephalosporin was statistically significantly lower in the MG (p=0.048 and p: 0.043, respectively), while colistin was statistically higher in the MG (p=0.005). In the MG, carbapenem resistance was observed in 25 (46.3%) patients (p=0.001).

**Table 1. Demographic and Clinical Characteristics, Underlying Diseases and Risk Factors with of patients with Carbapenem-Susceptible (CS) and Carbapenem-Resistance (CR) *Klebsiella spp*. infections**

| | CS group (n:250) | CR group (n:95) | p |
|---|---|---|---|
| Age, months (median [IQR]) | 17 (0-224) | 12 (1-216) | 0.9 |
| Gender, female/male | 109/141 | 43/52 | 0.78 |
| Underlying disease | | | 0.84 |
| Malignancy | 75 (30) | 33 (34.7) | |
| Immunosuppressed situations | 19 (7.6) | 5 (5.3) | |
| Neurologic/metabolic disorders | 62 (24.8) | 22 (23.2) | |
| Cardiovascular diseases | 26 (10.4) | 8 (8.4) | |
| Bronchopulmonary diseases | 9 (3.6) | 3 (3.2) | |
| Surgical conditions (e.g. burn, abdominal surgery) | 29 (11.6) | 15 (15.8) | |
| Other | 30 (12) | 9 (9.5) | |
| Type of infection | | | 0.08 |
| BSI | 126 (50.4) | 38 (40) | |
| CRBSI | 124 (49.6) | 57 (60) | |
| Wards, n (%) of patients | | | 0.1 |
| Pediatric intensive care unit | 77 (30.8) | 40 (42.1) | |
| Hematology oncology department | 66 (26.4) | 22 (23.2) | |
| Pediatric surgery unit | 23 (9.2) | 12 (12.6) | |
| Pediatrics department | 66 (26.4) | 14 (14.7) | |
| Pediatric burn unit | 7 (2.8) | 1 (1, .1) | |
| Pediatric bone marrow transplantation unit | 11 (4.4) | 6 (6.3) | |
| Indwelling devices, n (%) of patients | | | |
| Central venous catheter | 162 (64.8) | 70 (73.7) | 0.12 |
| Mechanical ventilation | 26 (10.4) | 29 (30.5) | **<0.001** |
| PEG tube feeding | 15 (6) | 61 (64.2) | **<0.001** |
| Urinary catheter | 31 (12.4) | 13 (13.7) | 0.75 |
| Neutropenic fever | 85 (34) | 35 (36.8) | 0.62 |
| Antibiotic use in the last 14 days, n (%) | | | |
| Yes | 81 (32.4) | 89 (93.7) | **<0.001** |
| Use of combined antibiotics | 15 (6) | 67 (70.5) | **<0.001** |
| Carbapenems | 19 (7.6) | 70 (73.7) | **<0.001** |
| Aminoglycosides | 12 (4.8) | 50 (52.6) | **<0.001** |
| β-lactam- β-lactamase inhibitor combinations | 26 (10.4) | 14 (14.7) | 0.26 |
| Cephalosporins | 34 (13.6) | 5 (5.3) | **0.03** |
| Glycopeptides | 7 (2.8) | 45 (47.4) | **<0.001** |
| Fluoroquinolones | 1 (0.4) | 3 (3.2) | **0.033** |
| Colistin | 2 (0.8) | 19 (20) | **<0.001** |

BSI: Bloodstream infection, CRBSI: Catheter-related bloodstream infection, PEG: Percutaneous endoscopic gastrostomy

**Table 2. Initial Laboratory Findings, Treatment of Patients with Carbapenem-Susceptible (CS) and Carbapenem-Resistance (CR) *Klebsiella spp*. infections**

| | CS group (n:250) | CR group (n:95) | p |
|---|---|---|---|
| Leukocyte* ($mm^3$) | 7820 (20-59090) | 7380 (10-29560) | 0.07 |
| Neutrophil* ($mm^3$) | 4260 (0-50310) | 3640 (0-24840) | 0.14 |
| Lymphocyte* ($mm^3$) | 1680 (0-10580) | 1820 (0-7710) | 0.16 |
| Thrombocyte* ($mm^3$) | 194 (2-1006) | 114 (9-1162) | 0.04 |
| CRP* mg/L | 60 (0-460) | 100 (0-321) | <0.001 |
| Duration of treatment for infection, days* | 14 (3-32) | 14 (1-40) | 0.03 |
| Time to provide culture negativity, days* | 2(1-10) | 3(0-7) | 0.002 |
| Microorganism | | | 0.09 |
| *K. pneumoniae* | 233 (93.2) | 93 (97.9) | |
| *K. oxytoca* | 17 (6.8) | 2 (2.1) | |
| Antibiotics used in treatment | | | |
| Carbapenems | 156 (62.4) | 61 (64.2) | 0.75 |
| Amikacin | 92 (36.8) | 32 (33.7) | 0.59 |
| Cephalosporins | 34 (13.6) | 7 (7.4) | 0.11 |
| Fluoroquinolones | 8 (3.2) | 7 (7.4) | 0.09 |
| Colistin | 21 (8.4) | 27 (28.4) | <0.001 |
| β-lactam- β- lactamase inhibitor combinations | 43 (17.2) | 9 (9.5) | 0.07 |
| Tigecycline | 1 (0.4) | 2 (2.1) | 0.12 |
| Use of combined antibiotics | 104 (41.8) | 50 (52.,6) | 0.07 |

CRP: C-reactive protein, *median (inter quartaile range)

**Table 3. Multivariate Analysis for Carbapenem Resistance**

| | OR | 95% CI | p |
|---|---|---|---|
| Thrombocyte ($mm^3$) | 0.997 | 0.995 - 1 | **0.037** |
| CRP (mg/dL) | 1.006 | 0.999 - 1.012 | 0.08 |
| Time to provide culture negativity, days | 1.191 | 0.814-1.745 | 0.37 |
| Mechanical ventilation | 0.231 | 0.017 - 3.111 | 0.27 |
| PEG tube feeding | 29.332 | 8.715 - 98.726 | **<0.001** |
| History of antibiotic use in the last 14 days | | | |
| Yes | 14.096 | 3.45 - 57.597 | **<0.001** |
| Use of combined antibiotics | 2.741 | 0.226 - 33.182 | 0.43 |
| Carbapenems | 3.154 | 0.744 - 13.362 | 0.12 |
| Aminoglycosides | 3.113 | 0.295 - 32.874 | 0.35 |
| Cephalosporins | 0.194 | 0.033 - 1.159 | 0.07 |
| Glycopeptides | 2.63 | 0.357 - 19.377 | 0.34 |
| Fluoroquinolones | | | 1 |
| Colistin | 2.365 | 0.132 - 42.506 | 0.56 |

CRP: C- reactive protein, PEG: Percutaneous endoscopic gastrostomy, OR: odds ratio, CI: confidence interval

| Table 4. Demographic, Clinical Characteristics and Laboratory Findings Characteristics of Patients According to Mortality | | | |
|---|---|---|---|
| | **Survival (n:291)** | **Death (n:54)** | **p** |
| Age, months* | 16.5 (0 - 224) | 25.5 (1 - 216) | 0.68 |
| Gender, F/M | 126/165 | 26/28 | 0.5 |
| Leukocyte* ($mm^3$) | 7750 (10-59090) | 8185 (10- 58460) | 0.77 |
| Neutrophil* ($mm^3$) | 4210 (0-50310) | 7389.4 (11146.1-0) | 0.4 |
| Lymphocyte* ($mm^3$) | 1715 (0- 10580) | 880 (10- 5930) | **0.016** |
| Thrombocyte* ($mm^3$) | 182 (2- 1162) | 39.5 (3-665) | **<0.001** |
| CRP* (mg/dL), (median(IQR)) | 60 (0-390) | 140 (12-460) | **<0.001** |
| Underlying disease | | | 0.2 |
| Malignancy | 89 (30.6) | 19 (35.2) | |
| Immunosuppressed situations | 21 (7.2) | 3 (5.6) | |
| Neurologic/metabolic disorders | 71 (24.4) | 13 (24.1) | |
| Cardiovascular diseases | 24 (8.2) | 10 (18.5) | |
| Bronchopulmonary diseases | 11 (3.8) | 1 (1.9) | |
| Surgical conditions (e.g. burn, abdominal surgery) | 40 (13.7) | 4 (7.4) | |
| Other | 35 (12) | 4 (7.4) | |
| Type of infection | | | **0.002** |
| BSI | 149 (51.2) | 15 (27.8) | |
| CRBSI | 142 (48.8) | 39 (72.2) | |
| Wards, n (%) of patients | | | **0.002** |
| Pediatric intensive care unit | 85 (29.2) | 32 (59.3) | |
| Haematology oncology department | 79 (27.1) | 9 (16.7) | |
| Pediatric surgery unit | 32 (11) | 3 (5.6) | |
| Paediatrics department | 74 (25.4) | 6 (11.1) | |
| Pediatric burn unit | 7 (2.4) | 1 (1.9) | |
| Pediatric bone marrow transplantation unit | 14 (4.8) | 3 (5.6) | |
| Microorganism, n (%) | | | 0.05 |
| *K. pneumoniae* | 272 (93.5) | 54 (100) | |
| *K. oxytoca* | 19 (6.5) | 0 (0) | |
| Indwelling devices, n (%) of patients | | | |
| Central venous catheter | 187 (64.3) | 45 (83.3) | **0.006** |
| Mechanical ventilation | 8 (2.7) | 47 (87) | **<0.001** |
| PEG tube feeding | 57 (19.6) | 19 (35.2) | **0.011** |
| Urinary catheter | 27 (9.3) | 17 (31.5) | **<0.001** |
| Neutropenic fever | 96 (33) | 24 (44.4) | 0.1 |

CRP: C-reactive protein, BSI: Bloodstream infection, CRBSI: Catheter-related bloodstream infection, PEG: Percutaneous endoscopic gastrostomy
*median (interquartile range)

| Table 4. Continued | | | |
|---|---|---|---|
| | **Survival (n:291)** | **Death (n:54)** | **p** |
| History of antibiotic use in the last 14 days, n (%) | | | |
| Yes | 133 (45.7) | 37 (68.5) | **0.002** |
| Use of combined antibiotics | 54 (18.6) | 28 (51.9) | **<0.001** |
| Carbapenems | 60 (20.6) | 29 (53.7) | **<0.001** |
| Aminoglycosides | 39 (13.4) | 23 (42.6) | **<0.001** |
| β- lactam- β- lactamase inhibitor combinations | 37 (12.7) | 3 (5.6) | 0.13 |
| Cephalosporins | 35 (12) | 4 (7.4) | 0.33 |
| Glycopeptides | 31 (10.7) | 21 (38.9) | **<0.001** |
| Fluoroquinolones | 2 (0.7) | 2 (3.7) | 0.06 |
| Colistin | 8 (2.7) | 13 (24.1) | **<0.001** |
| Antibiotics used in treatment | | | |
| Carbapenems | 185 (63.6) | 32 (59.3) | 0.55 |
| Amikacin | 111 (38.1) | 13 (24.1) | **0.048** |
| Cephalosporins | 39 (13.4) | 2 (3.7) | **0.043** |
| Fluoroquinolones | 12 (4.1) | 3 (5.6) | 0.64 |
| Colistin | 34 (11.7) | 14 (25.9) | **0.005** |
| β-lactam- β- lactamase inhibitor combinations | 48 (16.5) | 4 (7.4) | 0.09 |
| Tigecycline | 3 (1) | 0 (0) | 0.45 |
| Use of combined antibiotics | 132 (45.5) | 22 (40.7) | 0.52 |
| Carbapenem resistance | 70 (24.1) | 25 (46.3) | **0.001** |

CRP: C-reactive protein, BSI: Bloodstream infection, CRBSI: Catheter-related bloodstream infection, PEG: Percutaneous endoscopic gastrostomy
*median (interquartile range)

In the multivariate logistic regression analysis between clinical variables and mortality, lymphocyte counts (OR, 0.999: 95% CI, 0.999–1; p=0.011), CRP value (OR, 1.01: 95% CI, 1.002–1.019; p=0.017) and mechanical ventilation (OR, 1166,395: 95% CI, 130,601- 10417,014; p<0.001) were found to be independent predictors of mortality (Table 5).

## DISCUSSION

BSI are the most important and lethal complications of healthcare settings. The prevalence of CR gram-negative bacteria has increased dramatically in recent years.[3] There are increasing rates of resistance in *Klebsiella spp.,* like other resistant bacteria, due to many factors such as underlying diseases, prolonged hospitalization, use of broad-spectrum antibiotics, and presence of catheterization (central venous catheter, urinary catheter, etc.).[1,3] It is important to know the etiological and demographic characteristics, and predictive factors in children and to determine possible antibiotic susceptibility, because of the high mortality rates and the need for early treatment.

In this article, we report the clinical characteristics and outcomes of BSI caused by *Klebsiella spp.* in the largest children's hospital in Turkey. CR enteric bacteria, which started to be seen in Türkiye after 2010, became endemic throughout the country after 2014-2015. According to the 2020 report of the Central Asian and European Surveillance of Antimicrobial Resistance (CAESAR) study, the rate of carbapenem resistance in *K. pneumoniae* strains in Türkiye is 39%.[15-18] Studies have shown that higher resistance to carbapenems may be due to the fact that patients in reference hospitals are complicated patients with long hospital stays and/or are colonized with multidrug-resistant organisms (MDROs).

The rate of CR in BSI due to *Klebsiella* in children varies between 1% and 79% in publications. These rates vary over the years as well as according to patient characteristics.[9,19-22] Carbapenem resistance rate was 27.5% and the mortality rate was 15.7% in our study. In a study of 97 children with gram-negative bacteremia in Türkiye, carbapenem resistance (58.1%) in *Klebsiella spp.* and mortality rate (35.5%) in all CR gram-negative

| Table 5. Multivariate analysis for mortality | | | |
|---|---|---|---|
| | **OR** | **95% CI** | **p** |
| Lymphocyte ($mm^3$) | 0.999 | 0.999 - 1 | **0.011** |
| Thrombocyte ($mm^3$) | 1 | 0.996 - 1.004 | 0.87 |
| CRP (mg/dL) | 1.01 | 1.002 - 1.019 | **0.017** |
| Type of infection | 9.193 | 0.977 - 86.523 | 0.05 |
| Wards | 0.691 | 0.418 - 1.144 | 0.15 |
| Mechanical ventilation | 1166.395 | 130.601 - 10417.014 | **<0.001** |
| Presence of central venous catheter | 0.407 | 0.035 - 4.789 | 0.48 |
| PEG tube feeding | 1.001 | 0.15 - 6.67 | 1.00 |
| Presence of urinary catheter | 1.141 | 0.154 - 8.479 | 0.90 |
| Antibiotic use in the last 14 days | | | |
| Yes | 1.947 | 0.315 - 12.025 | 0.47 |
| Use of combined antibiotics | 0.313 | 0.011 - 9.214 | 0.50 |
| Carbapenems | 0.341 | 0.026 - 4.519 | 0.41 |
| Aminoglycosides | 0.537 | 0.055 - 5.204 | 0.59 |
| Glycopeptides | 9.026 | 0.924 - 88.162 | 0.06 |
| Fluoroquinolones | 2.726 | 0.003 - 2240.832 | 0.77 |
| Colistin | 2.904 | 0.236 - 35.755 | 0.41 |
| Antibiotics used in treatment | | | |
| Amikacin | 0.52 | 0.124 - 2.185 | 0.37 |
| Cephalosporins | 0.197 | 0.007 - 5.781 | 0.35 |
| Colistin | 0.368 | 0.067 - 2.023 | 0.25 |
| Carbapenem resistance | 0.45 | 0.055 - 3.693 | 0.46 |

OR: odds ratio, CI: confidence interval, CRP: C-reactive protein, PEG: Percutaneous endoscopic gastrostomy

infections were higher than in our study.[10] These results may be due to the larger number of patients in our study, but may also be explained by the realization of carbapenem resistance over the years and the earlier initiation of combination therapy. In order to better manage serious infections caused by resistant bacteria, the resistance status of microorganisms should be actively monitored and surveillance data should be regularly evaluated. In our hospital, we closely monitor data on these infections. Measures include isolating patients with antibiotic-resistant micro-organisms, closely monitoring the hand hygiene of the staff, and controlling inappropriate use of broad-spectrum antibiotics.

There are studies showing that prior use of carbapenems, colistin, cephalosporins, aminoglycosides, quinolones, and glycopeptides can increase carbapenem resistance.[1,10,18,19,23-25] In this study, we aimed to analyze the relationship between previous antibiotic use and CSI caused by *Klebsiella spp.* Recent antibiotic exposure was identified as a risk factor for BSI caused by *Klebsiella spp.* Previous use of carbapenems, aminoglycosides, glycopeptides, quinolones, and colistin was common in the CR group. Previous use of β-lactam β-lactamase inhibitor combinations did not differ in both groups, the history of cephalosporin use was more common in the carbapenem-sensitive group. Prior use of antibiotics, especially carbapenems, aminoglycosides, glycopeptides, and colistin increased the risk of mortality. This result may be related to the necessity of using broad-spectrum and multiple antibiotics other than cephalosporins since our patients were high-risk patients with an underlying disease and needed to take broad-spectrum antibiotics. In addition, prior use of cephalosporins in the CS group may be the result of using narrow-spectrum antibiotics as much as possible in our hospital.

In addition, determining the risk factors that increase the possibility of resistant bacterial infection is important for early treatment and reduction of mortality. There are publications that associate mechanical ventilation and total parenteral nutrition with mortality and infections due to resistant microorganisms in children.[9,24] In our study, PEG tube feeding was a risk factor for carbapenem resistance, while mechanical ventilation was a risk factor for mortality. Mechanical ventilation and PEG tube feeding were significantly higher in the CR and the MG. In this study, CRP elevation was higher in the CR group and MG group. CRP elevation can be remarkable in terms of carbapenem resistance and severe clinical course.

In our study, in addition to *K. pneumoniae*, BSI due to *K. oxytoca* was also present. *K. oxytoca* was responsible for 5.5% of the BSI, all of which were CS.

The recommended empirical, appropriate treatment option for infections due to resistant agents is still uncertain and depends primarily on the susceptibility pattern of each isolate.[10,26] Some studies have shown that combination therapy is more effective than monotherapy.[10,26,27] Some previous studies have concluded that carbapenem-based combination therapy is the most effective treatment option for carbapenem-producing *K. pneumoniae*.[10,26-28] In the present study, prolonged carbapenem infusion therapy rates were also high in CR cases. Colistin and tigecycline have also been used alone or in combination in some studies.[10,27,29] Combination therapy with colistin and/or tigecycline may have a survival benefit. Furthermore, the use of these drugs is debated due to the increasing resistance rates in complicated and severe patients.[28,30] In this study, carbapenem resistance, and mortality were found to be higher in patients with previous colistin treatment. In addition, the CR group had to use colistin more frequently in the treatment, and the mortality rate was higher in the patients who used colistin in their treatment. Colistin treatment was not an independent risk factor for mortality.

Mortality was higher in CRBSI than in BSI. It is necessary to terminate the use of the catheter in the early period of catheter infections, especially with resistant agents, and to understand the importance of catheter care.

This study has several limitations. Since the study was retrospective, the data were obtained from patient records, so there are inevitably some missing data. In addition, our data are from a single-center study. Multi-center studies may help to clarify demographic and epidemiological characteristics and avoid statistical limitations. The data also lack genotyping and molecular analysis. If available, these would be very valuable.

## CONCLUSION

In many studies, CR *Klebsiella spp*. is the main and serious cause of BSI infections in children. To our knowledge, our study is the largest single-center study of *Klebsiella* infection in pediatric patients. Mechanical ventilation, PEG tube feeding, and previous antibiotic use, especially carbapenems, aminoglycosides, aminoglycosides, glycopeptides, fluoroquinolones, and colistin were found to strongly influence the development of BSI with CR *Klebsiella spp*. Thrombocytopenia, elevated CRP, CRBSI, use of indwelling devices, previous use of antibiotics (carbapenems, aminoglycosides, glycopeptides, colistin), and carbapenem resistance increased the risk of mortality due to *Klebsiella* related BSI. CR Klebsiella spp. infections are serious infections, the likelihood of resistance is difficult to predict and treatment options are limited. Narrow-spectrum targeted antimicrobial therapies and minimally invasive procedures can be important steps in the hospital stewardship.

### Ethical approval

This study has been approved by the Ankara City Hospital Clinical Research Ethics Committee (approval date 29.09.2021, number E2-21-718). Informed consent was not required because of the retrospective design.

### Author contribution

Surgical and Medical Practices: AY, GİB, EA, BNA; Concept: AY, MYG, SK; Design: AY, SK, SKY, BG, AÖP; Data Collection or Processing: EA, MYG, BNA, SK; Analysis or Interpretation: AY, GİB, SKY, BG, AÖP; Literature Search: GİB, SKY, BG, AÖP; Writing: AY, GİB. All authors reviewed the results and approved the final version of the article.

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### Conflict of interest

The authors declare that there is no conflict of interest.

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Case Report

# Extended oligoarticular juvenile idiopathic arthritis with multiple enchondromatosis: A case report

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## ABSTRACT

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease in childhood. Since there is no pathognomonic diagnostic criterion, the diagnosis is made by excluding other arthritis in childhood. Multiple Enchondromatosis, also known as Ollier's disease, is an ossification disorder often seen in the metaphyseal and diaphyseal regions of long bones or the metaphyseal regions of tubular bones in the hands and feet. Pain, shortening, deformity, fracture, and transformation into malignancy may appear. Here we report a case with extended oligoarticular juvenile idiopathic arthritis (oligo JIA) who developed enchondromatosis during clinical follow-up. While the patient was in remission without medication, he presented with swelling in the hand fingers and enchondromatosis lesions with expansile lytic characteristics were seen on the radiograph. Comorbid diseases can be added in the clinical follow-up of JIA patients. Physical examination is important in terms of added comorbid disease. Our case report is important because it is the first case in which these two diseases are seen together in the literature.

**Keywords:** Deformity, enchondromatosis, Juvenile Idiopathic Arthritis

## INTRODUCTION

Juvenile idiopathic arthritis (JIA) is defined as a heterogeneous group of diseases that includes arthritis that begins before the age of 16 and lasts longer than 6 weeks. It is the most common chronic rheumatic disease in childhood.[1] The diagnosis of JIA is based on the exclusion of other causes of chronic arthritis in childhood.[2] According to the International League of Associations for Rheumatology (ILAR) classification, JIA is classified into 7 subgroups based on clinical and laboratory findings in the first 6 months. Oligoarticular juvenile idiopathic arthritis (Oligo JIA), described as 4 or fewer joint involvement during the first 6 months of the disease, accounts for 50-80% of all JIA patients. Persistent type is described as four or fewer joints involved during the all disease course. The extended type is described as more than 5 joints involved after the first 6 months.[3]

Multiple enchondromatosis was described by Ollier in 1899. It is an ossification disorder often seen in the metaphyseal areas of the tubular bones or in the metaphyseal and diaphyseal areas of the long bones. Enchondromas can cause pain, shortening, deformity, and fractures in the bones.[4] Transformation to chondrosarcoma is observed in approximately 20-50% of cases.[5]

## CASE REPORT

A seven-year-old male patient presented with pain and swollen knees at the age of 2. He has been suffering from bilateral knee

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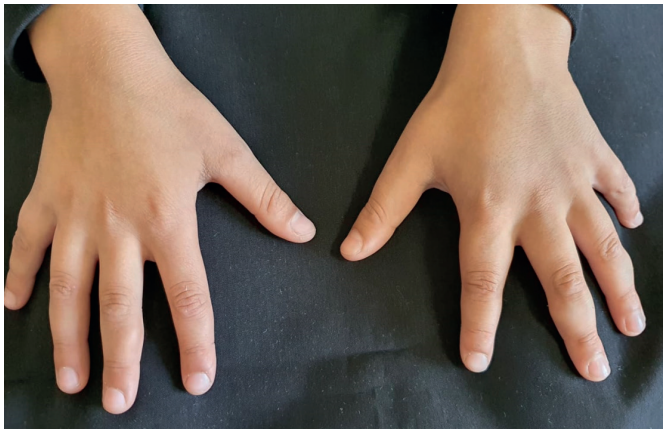

**Figure 1.** Swelling in the 3th finger of the right hand, the 3th and 4th fingers of the left hand.

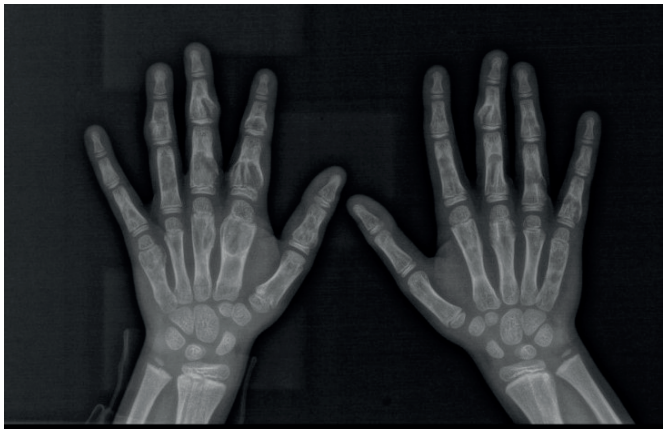

**Figure 2.** Expansile lytic lesions in the medullary area in the metaphysodiaphyseal area on both metacarpals and phalanges (predominantly in the proximal and middle phalanges).

arthritis for 2 months. His erythrocyte sedimentation rate (ESR) was 67 mm/h, C-reactive protein (CRP) was 15.59 mg/L, anti-nuclear antibody (ANA) was 1/1000, Rheumatoid Factor was 6.1 IU/mL, and HLA B27 was negative. Knee ultrasonography showed bilateral massive suprapatellar effusion. The patient was diagnosed with oligo JIA and treated with intra-articular steroid injection in bilateral knee joints. Both ankles and wrist joints were involved after one year. Because of the increased number of articular involvement, the patient was diagnosed with extended oligo JIA. The patient was treated with methotrexate. Methotrexate was discontinued after one year of remission. After three years of remission, the patient was admitted with swelling and deformity on the fingers. His physical examination showed expansion and deformities on the right 3rd middle

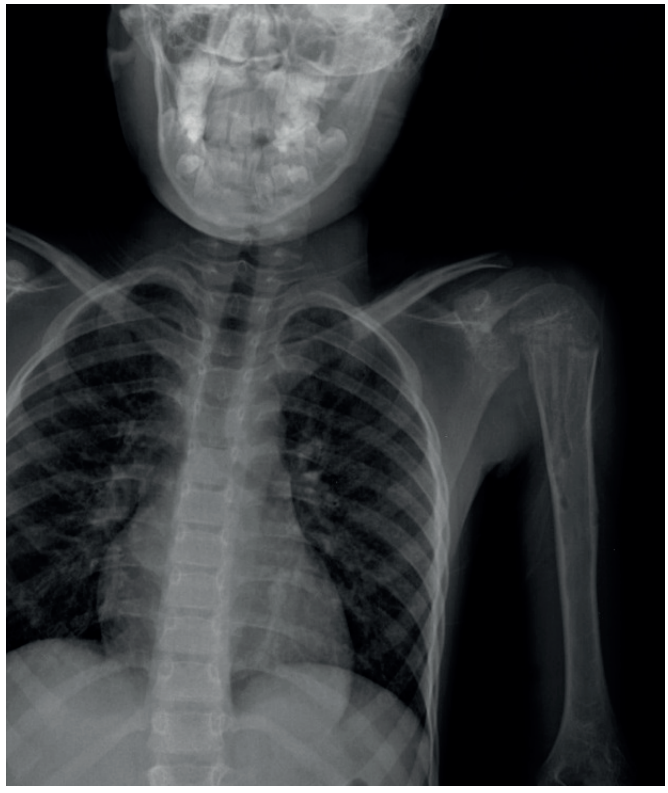

**Figure 3.** A lytic lesion in the medullary area extending to the left humerus proximal metaphysodiaphyseal area.

phalanx and left 3rd and 4th middle phalanges (Figure 1). The systemic and joint examinations were normal. The radiographic examination revealed expansile lytic lesions in the medullary area at the metaphysodiaphyseal area in the metacarpals and phalanges of both hands (Figure 2) and on the left humerus proximal metaphysodiaphyseal area (Figure 3). The patient was diagnosed with multiple enchondromatosis after radiographic examination.

## DISCUSSION

We presented the case of a patient with extended oligo JIA and concomitant multiple enchondromatosis. Juvenile idiopathic arthritis is the most common chronic rheumatic disease in childhood. If not treated early and properly, it can cause severe deformity and disability. Non-steroid anti-inflammatory drugs, intraarticular and systemic corticosteroids, methotrexate, and biological drugs are used for treatment.[6]

Multiple enchondromatosis is a non-hereditary bony deformity that is most commonly seen in the tubular bones of the hand and foot and in the metaphyses of long and flat bones. Expansive masses and deformities occur as a result of the proliferation

of cartilage cells.[7] The disease affects both genders and all age groups. Small tubular bones of the hand are involved in 40-65% of cases; mass formation is mostly seen in the proximal phalanges, metacarpals, middle phalanges, and distal phalanges, respectively.[8] Our case also presented the involvement of fingers, which is consistent with the literature.

Juvenile idiopathic arthritis is characterized by periods of remission and activation. While some JIA subtypes have inactive diseases with treatment, some subtypes have inactive diseases without treatment.[9] Deformities may develop in patients who have persistently active diseases or who do not receive appropriate treatment. Finger deformities can be detected in inflammatory rheumatic diseases, especially polyarticular JIA, and in non-inflammatory conditions. Non-inflammatory diseases such as mucopolysaccharidosis, skeletal dysplasias, and pachydermodactyly can cause deformities.[10] Our case also presented with finger deformities during the follow-up remission period. Our patient had extended oligo JIA, and the metacarpophalangeal and proximal interphalangeal joints could be involved in the disease course. However, the absence of arthritis findings on physical examination and the detection of multiple enchondromas on the radiographs showed that a new comorbid disease was added. A good physical examination and advanced radiological imaging are necessary for the differential diagnosis. We diagnosed the disease by direct radiographs showing expansile lytic lesions on the fingers and humerus. Patients with multiple enchondromatosis may require surgical intervention for pathological fracture, deformity, or suspected malignant transformation.[11]

Our patient is the first case diagnosed with extended oligoarticular JIA and enchondromatosis together. This patient should be followed up for possible complications and malign transformation.

### Ethical approval

The patient's parents provided informed consent for the publication of the report.

### Author contribution

Surgical and Medical Practices: AYB, EK, ZFK, APK, MHP; Concept: APK, MHP; Design: APK, MHP; Data Collection or Processing: AYB, EK; Analysis or Interpretation: AYB, ZFK; Literature Search: AYB; Writing: AYB, APK. All authors reviewed the results and approved the final version of the article.

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### Conflict of interest

The authors declare that there is no conflict of interest.

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