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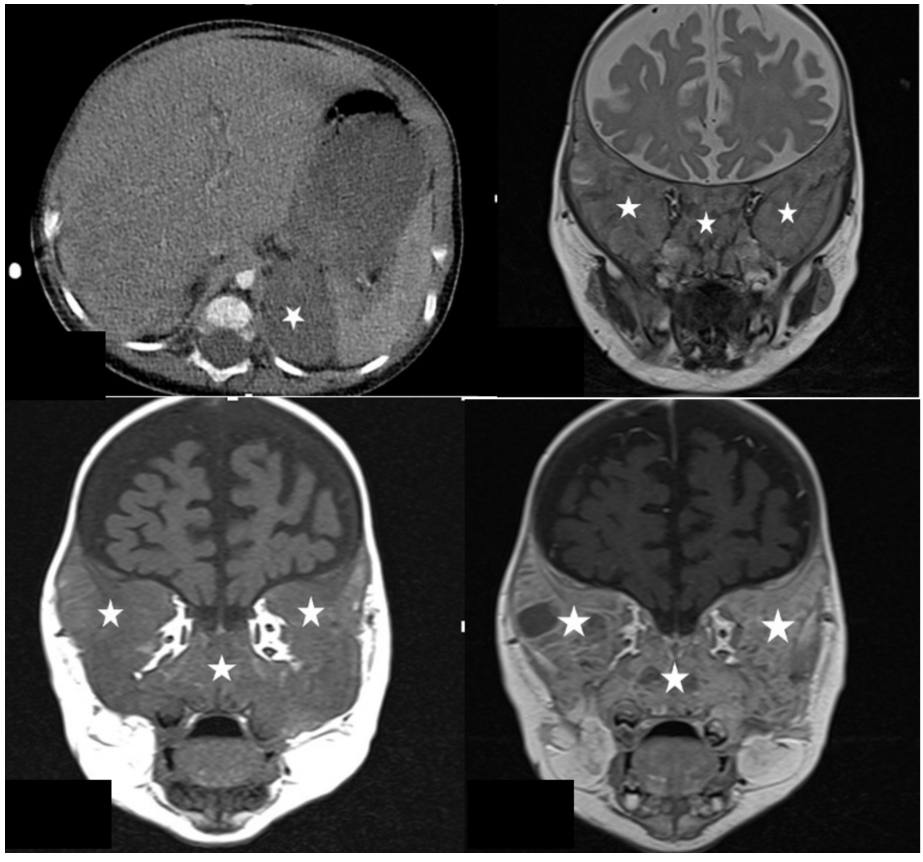

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Review

Approaching a Newborn with Atypical Genitalia: Hints for Pediatricians

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ABSTRACT

Infants born with genitals that do not appear typically male or female, are classified as having a difference/disorder of sex development (DSD). The current terminology and classification of DSD was established as suggested in the Chicago consensus statement in 2006. According to this consensus, patients with a DSD diagnosis are divided into three karyotype-based subgroups: 46,XY DSD; sex chromosome DSD, and 46,XX DSD. A newborn with DSD must be evaluated timely by a multi-disciplinary team including endocrinologist, psychologist, and urologist. The reason for this is two-fold: 1st to assign an appropriate sex of rearing to the infant based on the etiology of the condition and associated medical and psychosexual outcomes, and 2nd to detect any underlying life-threatening disorder if present. Neonates with ambiguous genitalia have various clinical presentations, etiologies, and outcomes. Furthermore, family adjustment and the degree of involvement of health professionals in psychosocial aspects of the condition affect health-related quality of life more than other congenital problems in DSD. For this reason, establishing correct communication with the patient and his/her family and providing appropriate information play a central role in DSD management and correct diagnosis and correct treatment. This review provides some clinical clues about the history, physical examination and laboratory and imaging characteristics of a newborn with DSD, which can allow for timely diagnosis, treatment and family counseling. We also emphasize some important points for an appropriate initial communication with the family of a patient with DSD.

Keywords: Disorders of sexual development, atypical, ambiguous, genitalia

INTRODUCTION

Atypical or ambiguous genitalia basically involves virilization of female genitalia or undervirilization of male genitalia. It is critically important to determine the etiology as quickly as possible when genital ambiguity is noticed. Besides the parental stress due to the unclarity of the condition, ambiguous genitalia may constitute a signal of a medical emergency, including adrenal insufficiency or of an important disorder of the kidneys or the urogenital system. Therefore, the initial evaluation must assess whether there are such disorders accompanying ambiguous genitalia. There are many different diagnoses that can result in atypical genitalia. The local team plays key roles in the initial management and providing support for the parents. Language needs to be used carefully with particular clarity when liaising with parents and local health professionals. Clinical findings should guide the initial investigations. The current article provides an initial approach to the management of a baby born with atypical or ambiguous genitalia.

Sex Development and Typical Genitalia in Males and Females

Gender is not only the structure suggested by the external sex organs but also a whole that includes chromosomes, sex-determining genes, gonadal histology, hormones and anatomy of internal genital organs.

Human sex development occurs in 3 basic steps: 1) It is the "chromosomal sex" that occurs with fertilization. Whether the

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spermatogonia that fertilize the ovum have X or Y chromosomes determine the chromosomal sex. 2) The second step is to determine the "gonadal sex". That is, it is the transformation of the undifferentiated gonad into the testis or ovary. Sex determination is the formation of a testis or an ovary from an undifferentiated bipotential gonad and is driven by the sequential expression of many genes. 3) The differentiation of the internal and external genital organs by the hormones secreted from the testis determines the "phenotypic sex". Anti-Müllerian hormone (AMH) synthesized in Sertoli cells causes regression of Müllerian structures. In the absence of AMH, the fallopian tubules, uterus, and upper 1/3 of the vagina are formed. Testosterone is produced from Leydig cells and stabilizes Wolffian ducts to form epididymis, vas deferens and seminal vesicles. Testosterone is converted to dihydrotestosterone, which provides virilization of the external genitalia. Again, insulin-like factor 3 secreted from Leydig cells is a peptide hormone that ensures the descent of the testis into the scrotum[1]. It is been known for many years that the genital primordium develops toward the female phenotype in case of a lack of testicular hormones[1]. Environmental factors, hormones and socio-cultural variables constitute male or female behavior, that is, "psychological sex"..."

To appreciate the various genital phenotypes associated with ambiguity, it is important to first define typical genitalia for males and females, respectively. A full-term male infant is expected to have bilateral testicles that are descended, complete formation of scrotal folds including midline fusion, and a typical size penis (average penile length is between 2.5-4.5 cm, for a full-term infant), including well-formed corporal bodies and a urethral meatus located at the tip. A full-term female infant is expected to have bilateral separation of the labial folds, no palpable gonads, and separate urethral and vaginal openings. The average clitoral length and width for a full-term infant girl born was between 2-8.5 mm.

Conditions where the chromosome structure, gonads, or external genitalia are incompatible or atypical are defined as disorders/ differences of sex development (DSD). The classification of DSD was proposed at the first international consensus in 2005 and based mainly in the chromosomal constitution[2,3] (Table 1).

46,XY infant with bilateral cryptorchidism, bifid scrotum and hypospadias, or isolated penoscrotal hypospadias, should be investigated for DSD. Isolated undescended testes were more frequent in preterm males. Isolated micropenis (<2.5 cm), if both testes are descended and normal in size, is not considered a presentation of ambiguous genitalia. The penis may falsely appear smaller simply because of a suprapubic fat pad, thus palpation of size, corporal volume and consistency is important. Penis size varies among various populations and changes according to gestational age and can be assessed using reference charts[4,5]. Similarly, distal hypospadias with no other atypical genital features in males are not usually indicative of DSD[6]. For a 46,XX infant, clitoromegaly (>1 cm) labial fusion or palpable gonads in what appears to otherwise be typical female external genitalia should be investigated further. Perceived clitoromegaly is not usually associated with an underlying DSD if the newborn is born prematurely. The labia minora can be prominent in the female preterm infants with little subcutaneous fat, but without no labioscrotal in the absence of excess androgen. The clitoral skin may also be misinterpreted as clitoromegaly[2].

Management

History

Important questions guiding the diagnosis and management are listed below:

* Drugs used in pregnancy
* Maternal virilization during pregnancy, for example, voice change and hirsutism (important for the diagnoses of maternal virilizing tumours, P450 oxidoreductase deficiency or placental aromatase deficiency)
* Consanguinity (as many of the causes of ambiguous genitalia have a genetically inherited)
* History of previous unexplained neonatal deaths, ambiguous genitalia, infertility, or genital surgery in the family.

Physical Examination

There are numerous important points to consider while examining a newborn with ambiguous genitalia that may help in differential diagnosis:

* As in all newborns vital signs including blood pressure, capillary refill and heart rate should be checked. Excessive pigmentation (areolar, genital or diffuse pigmentation) should be noted. These are particularly important for DSD etiologies related to adrenal insufficiency.
* Midline defects (cleft lip/palate), and dysmorphic features, and other associated renal, cardiac, and skeletal features may help guide etiologic diagnosis.
* Palpation of the gonads, in the labioscrotal folds or along the inguinal region. A palpable gonad usually implies the presence of a Y chromosome and a testicular tissue on that gonad, rarely the gonad could still be an ovary or ovotestis where a testicular tissue is present in the same gonad. A baby with asymmetric genitalia may also suggest chromosomal mosaicism such as 45,X/46,XY karyotype (mixed gonadal dysgenesis). These babies present with substantial phallic enlargement and hypospadias and a palpable testis in the labioscrotal fold on one side but no palpable gonad on the other side. At laparoscopy, a streak gonad and hemi-uterus are typically identified on the side contralateral to the descended or palpable gonad.
* Length and size (diameter) of phallus should be measured.
* Degree of labial fusion and measurement of anogenital distance are noted to assess prenatal androgen exposure.
* Position and number of urethra/urogenital sinus openings are recorded. Severe hypospadias can develop because of

Table 1. Classification of DSD	
Sex chromosomal DSD	
45,X0	Turner syndrome and variants)#
47,XXY	(Klinefelter syndrome and variants)
45,X/46,XY and 46,XX/46,XY	(Mixed gonadal dysgenesis, gonadal chimerism)
46,XX DSD	
Disorders of gonadal development	• (Ovo) testicular DSD
	• Monogenic forms of primary ovarian insufficiency (mutations in genes involved in gonadal (ovarian) development; ie *NR5A1* and *WT1*)
	• Syndromic forms
Disorders of androgen excess	• Aromatase (CYP19A1) deficiency
	• Congenital adrenal hyperplasia (mutations and/or deficiencies in CYP21A2, HSD3B2, CYP11B1 and POR)
	• Luteoma
	• Iatrogenic
Unclassified disorders	• MRKH type I and II syndrome
	• Complex syndromic disorders
46,XY DSD	
Disorders of gonadal development	• Complete or partial gonadal dysgenesis, monogenic forms (for example, SRY, NR5A1 and WT1)
	• Testicular regression
	• Ovotesticular DSD
	• Syndromic forms
Disorders of androgen synthesis	• Associated solely with androgen biosynthesis defects (mutations or deficiencies in HSD17B3 and SRD5A2, for example)
	• Associated with congenital adrenal hyperplasia and early androgen biosynthesis defects (mutations and/or deficiencies in STAR, CYP11A1, HSD3B2, POR and CYP17A1)
	• Associated with placental insufficiency or endocrine disruption
	• Syndromic forms (for example, Smith-Lemli-Opitz)
Disorders of androgen action	Complete and partial androgen insensitivity
Persistent Müllerian duct syndrome	Due to mutations or deficiencies in *AMH* and *AMHR2*
Unclassified disorders	• Hypospadias of unknown origin
	• Epispadias
	• Complex syndromic disorders

MRKH: Mayer-Rokitansky-Küster-Hauser syndrome, DSD: Disorders/differences in sex development, AMH: anti-Müllerian homone

3β-hydroxysteroid dehydrogenase deficiency, partial androgen insensitivity, 5-alpha reductase deficiency in up to 40% the cases[7].

A five-stage Prader grading system is used to describe the degree of genital atypia and degrees of virilization[8] (Figure 1):

Stage 1: Clitoromegaly without labial fusion.

Stage 2: Clitoromegaly with posterior labial fusion.

Stage 3: Significant clitoromegaly, single perineal urogenital orifice, almost complete labial fusion.

Stage 4: Phallic clitoris, urethra like urogenital sinus at the base of clitoris, complete labial fusion.

Stage 5: Penile clitoris, urethral meatus at the tip of the phallus, scrotum-like labia (appearance of bilaterally cryptorchid male).

A Quigley grading system from grades 1 through 6 is used to describe the degree of genital atypia in androgen insensitivity[9] where grade 1 indicates a fully masculinized external genitalia, grade 6 indicates fully feminized genitalia and grades 2 through 5 qualify as increasingly feminized genitalia. Recently, some other scoring systems were developed to assess external genital masculinization in detail including external masculinization score

Table 2. External musculinisation score					
Scoring	**Scrotal fusion**	**Micropenis**	**Urethral meatus**	**Right gonad**	**Left gonad**
3	Y	N	Normal		
2			Distal		
1.5				Labioscrotal	Labioscrotal
1			Mid	Inguinal	Inguinal
0.5				Abdominal	Abdominal
0	N	Y	Proximal	Absent	Absent
A score <11 out of 12 needs further investigation					

Table 3. Initial investigations in a newborn with atypical/ambiguous genitalia	
Investigation	**Comment**
Karyotype/FISH or PCR for *SRY*	Karyotype should be studied for each case with a suspicion of DSD. The result of a formal karyotype can be obtained in 2-3 weeks. A fluorescent *in situ* hybridisation (FISH) or PCR for *SRY* gene is more rapid to have an information for the existence of Y chromosome in the karyotype.
ACTH, electrolytes, blood sugar, 17-OH progesterone, renin, blood pressure monitoring	To assess adrenal insufficiency, especially CAH. Salt-wasting generally starts after first week of life in the majority of cases with CAH adrenal insufficiency. Adrenal steroid measurements are suggested to perform after 2nd postnatal day. High dose synacthen testing to assess glucocorticoid synthesis may be needed.
Pelvic USG for Müllerian structures, adrenals (presence? enlarged?) and gonads (including examination of the inguinal canal and labial folds for the gonads)	Inguinal or labial gonads suggest the presence of functional testis and Y chromosome, presence of unilateral or bilateral Mullerian structures suggests absence of functional testicular tissue on the same side.
Urinanalysis, urine protein creatinine ratio	Important for identifying additional renal abnormalities or some etiologies associated with severe renal involvement (eg associated oliguria, proteinuria or hematuria may suggest *WT1* mutations). A renal USG can be needed in selected cases.
FSH, LH, testosterone, anti-Müllerian hormone	To investigate the function of gonads. These tests provide useful information particularly after 1-2 weeks of life, during the minipuberty period. Low AMH, high FSH and low testosterone in a 46,XY patient suggests a gonadal dysgenesis. Normal AMH concentration excludes gonadal dysgenesis.
ACTH: Adrenocorticotropic hormone, AMH: anti-Müllerian hormone, CAH: Congenital adrenal hyperplasia, USG: Ultrasound, DSD: Disorders/differences in sex development	

(EMS) (Table 2)[10]. The EMS was modified as external genital scores to be used for external genitalia in premature and term babies up to 24 months[11].

* Clitoral enlargement with or without hypospadias but with impalpable gonads in hyperpigmented genitalia should suggest congenital adrenal hyperplasia (CAH) until proven otherwise. CAH secondary to 21-hydroxylase deficiency is the most common cause of such a presentation, followed by 11β-hydroxylase deficiency.

* A typical female genital should be further investigated for DSD in 2 important clinical scenarios:

1. A female presenting with severe adrenal insufficiency (This suggests etiologies that cause severe impairment of adrenal and gonadal steroidogenesis such as *StAR* and *CYP11A1* gene mutations in a 46,XY patient).
2. Inguinal herniae in an clear female baby who was found to have a gonad found in the hernial sac at surgery. This presentation may indicate 46,XY gonadal dysgenesis, 17β-hydroxysteroid dehydrogenase deficiency, and 5-alpha reductase deficiency and CAIS.

Laboratory Assessment and Imaging

A list of the initial laboratory and imaging assessments is provided in Table 3. A simplified diagnostic approach is shown in Figure 2.

Communication with the Family/Parents

When a baby is born with ambiguous genitalia, it is common for parents to describe the initial meeting with a health professional as an indelible and sometimes traumatic memory. Poor communication or incorrect use of language at this time can have long-lasting consequences. It is, therefore, wise to think about terminology and content in advance[12-16].

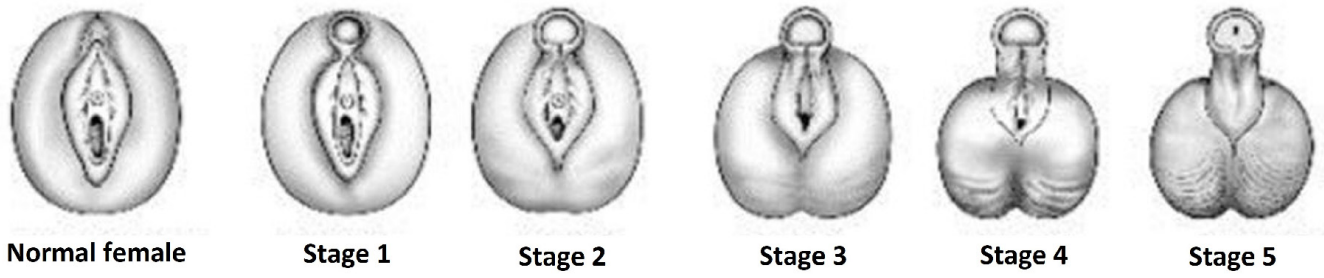

Figure 1. Prader scale of genital virilization

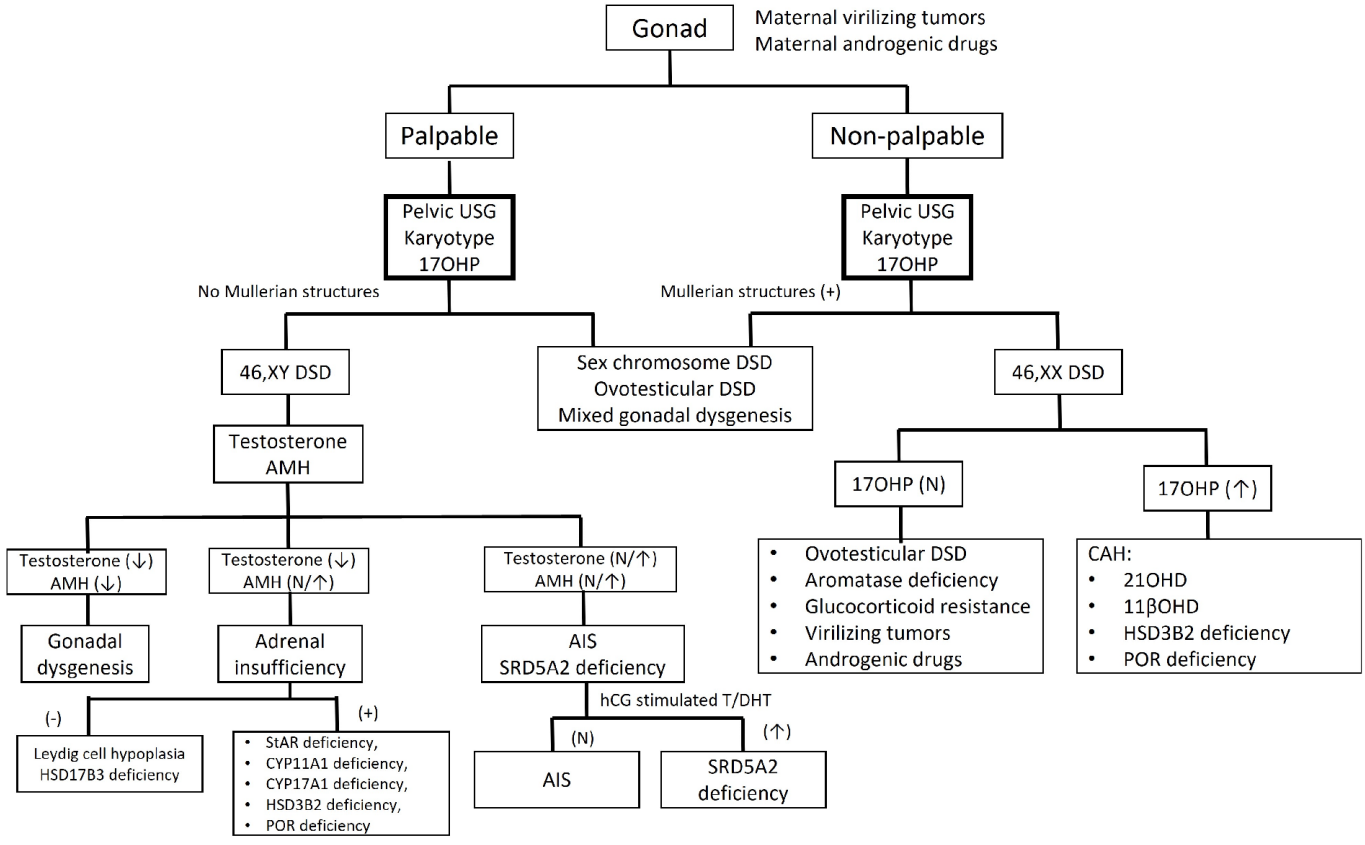

Figure 2. Flowchart for the differential diagnosis of DSD

DSD: Disorders/differences in sex development, 17OHP: 17OH-Progesterone, AMH: Anti-Müllerian hormone, USG: Ultrasound, AIS: Androgen insensitivity syndrome, SRD5A2: 5-alpha reductase, 21OHD: 21-alpha-hydroxylase, 11βOHD: 11β-hydroxylase, POR: P450 oxidoreductase

* It is appropriate for the most experienced "multidisciplinary team representative" to give the first speech with the family.
* The positive findings should be emphasized by the parents first, for example, congratulating the parents on the arrival of their baby and reporting all the normal findings from the examination.
* It is important to avoid terms such as "your daughter/son" that would suggest gender.
* Estimated or probable diagnoses and approaches should never be mentioned, particularly in the first conversation.
* First information can be given as "There is a problem/delay related to the development of your baby's reproductive system, so we cannot answer this question by just examining it. You will be given much a more comprehensive and reliable information at every stage with detailed blood and imaging tests". "Examinations and evaluations will be carried out in detail and carefully by a team of specialist doctors".

* In the examination process, it is suggested to provide information about not naming the baby.
* It is important to convey the message that as a multidisciplinary DSD management team, we understand the family`s situation very well, to make the family feel that we are willing to listen and, if necessary, to talk again about matters that are not understood.
* It should be emphasized that the most important issue is that the baby needs parents like all other healthy babies and that baby's care should be done without interruption.
* If the baby is to be examined, it should be accompanied by the parents.
* It should be respectful to the socio-cultural dynamics within the family, expectations and concerns should be listened to.
* Confidentiality should be respected during the genital examination.
* Disturbances in genital development can be explained by simple drawings in the following conversations.
* Confusing terminology, including bisexual, etc. should definitely be avoided.

Developing a plan early during treatment so that all information is provided to children gradually but ultimately fully is an important aspect of optimal DSD care.

The physician's desire to inform the child sometimes encounters resistance from the parents. This resistance results from parents who mistakenly believe that hiding details will protect their children from harmful information. The process of informing can be made more difficult, as conceptualizations and values about gender and sexuality vary greatly across cultures. The child's age and mental development status are decisive in the process of sharing information. Compared with children who are ignorant or misinformed about their situation, children who receive timely education will have better opportunities to develop adaptive coping skills, including expectations for a positive self-image and a fulfilling adult life despite bodily limitations.

Ethics

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Original Article

The Relationship Between Aboriginal and Rh Blood Types and Cow's Milk Protein Allergy

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ABSTRACT

Objective: Cow's milk protein allergy (CMPA) is the most common type of food allergy among infants. Several studies have found an association between Aboriginal blood types and allergies such as allergic rhinitis, asthma, and atopic dermatitis, but the role of blood type differences in cases of IgE-mediated CMPA and food protein-induced-allergic proctocolitis (FPIAP) is not known yet.

Methods: A total of 100 patients born in our hospital approximately 2017-2021 and followed up in our Paediatric Allergy Clinic with the diagnosis of IgE-mediated CMPA and FPIAP, and as the control group, 259 children born in our hospital who had no family history of atopy and no signs of allergic disease in the follow-up were included in the study. Blood types of healthy children, and those with IgE-mediated CMPA and FPIAP diagnosis were compared.

Results: One hundred patients with CMPA were included in the study. The mean age of these patients was 10.8 months, and 49% (n=176) were male. 57% of the patients were followed up with a diagnosis of IgE-mediated CMPA and 43% with FPIAP. Familial atopy accompanied 23% (n=23) of the cases with CMPA. There was no statistically significant difference between the distribution of Aboriginal and Rh blood types between the cases with CMPA and the control group ($p>0.05$). Additionally, there was no significant difference in blood type comparisons of the cases followed up with the diagnosis of IgE-mediated CMPA and FPIAP ($p>0.05$).

Conclusion: As far as we know, this is the first study of investigating the relationship between the blood type distribution of patients with CMPA and healthy subjects. To comprehend the role of blood type in the pathogenesis of CMPA and investigate the effect of blood types on tolerance development in CMPA cases, we think prospective studies with wider groups are necessary.

Keywords: Cow's milk protein allergy, Aboriginal blood type, Rh blood type, tolerance

INTRODUCTION

Cow's milk protein allergy (CMPA) is the most common type of food allergy in infants.[1] CMPA occurs through three types of immune mechanisms. Immunoglobulin E (IgE)-mediated reactions are characterized by acute symptoms involving one or more target organs such as the skin, respiratory system, and gastrointestinal tract. The non-IgE-mediated form are late-onset reactions with clinical manifestations such as enterocolitis or proctocolitis. There is also the "mixed type" in which both reactions are involved. This occurs with clinical findings such as atopic dermatitis and eosinophilic gastroenteropathy.[1-3]

Food protein-induced-allergic proctocolitis (FPIAP) is one of the non-IgE-mediated food allergies.[4,5] FPIAP is a disease characterized by immune response triggered by the intake of allergen food proteins from breast milk and inflammatory changes in the rectum and distal sigmoid colon.[6] It is a benign disease that usually starts

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in the first months of life and characterized by bloody stools in well-appearing infants, and one of the major causes of colitis in infants younger than one year old.[4,5,7]

The distribution of blood types can be affected by race, ethnicity, geographical conditions, and genetic reasons.[8] Blood types play a role in immunity. Additionally, many relationships have been shown between cardiovascular diseases, cancers, and autoimmune diseases and blood types.[9,10] There are few studies investigating the effect of blood types on allergic diseases. Data are unexpected, especially in the childhood age group. In a few studies conducted to date, allergic rhinitis is mostly associated with B and A blood types[11-14], asthma with 0 blood type[15-18] and A blood type[19], atopic dermatitis with 0 blood type.[20,21] However, the role of blood type differences in IgE-mediated CMPA and FPIAP cases is not known yet.

There is no study in the literature investigating the distribution of blood types in patients with CMPA. In this study, it was aimed to investigate the relationship between Aboriginal and Rh blood types and CMPA.

MATERIALS AND METHODS

Study Population

The study included 100 cases born in our hospital, followed up in our Paediatric Allergy Clinic with the diagnosis of IgE-mediated CMPA and FPIAP, and 259 healthy children, who were born in our hospital as the control group, with no family history of atopy and no signs of allergic disease in the follow-up. The clinical and laboratory results of the patients were recorded retrospectively from their file records. The presence of food sensitivity was evaluated with skin prick test and food-specific IgE (sIgE) test. In IgE-mediated CMPA cases, the diagnosis of cases without anaphylaxis was confirmed with an oral food challenge test (OFC).[2] The diagnosis of FPIAP was established in a patient who developed bloody stool after ingestion of suspicious food in accordance with the European Academy of Allergy and Clinical Immunology guideline, with the regression of his symptoms after the elimination diet and the recurrence of symptoms after the OFC test.[4] Aboriginal and Rh blood types of healthy children and blood types of patients with IgE-mediated CMPA and FPIAP were compared.

Patients with missing data in the file, patients whose diagnosis of CMPA could not be proven by performing an OFC test after elimination, infection leading to bloody diarrhea, anal fissure, perianal dermatitis/excoriations, intussusception, coagulation defects, necrotizing enterocolitis, inflammatory bowel disease, vitamin K deficiency, cases with diseases such as immunodeficiency, and cases with underlying chronic gastrointestinal system disease were excluded from the study. Informed consent was acquired from the parents of all patients who were then approved by the Research Ethics Committee of İstanbul Medipol University Hospital. Local ethics committee approval was obtained from Non-Invasive Clinical Research Ethics Committee of İstanbul Medipol University for the study (E-10840098-772.02-2630/21.01.2021, decision no: 84).

Evaluation of Laboratory Parameters

Aboriginal and Rh Blood Types

Blood type typing was determined using the gel centrifugation method with the DiaClon ABO/Rh for New-borns DVI+ monoclonal Ab kit (Bio-Rad, Cressier, Switzerland).

Skin Prick Test

The skin prick test was performed on all patients with fresh food (one drop of each fresh milk containing 3.5% fat) and commercial extracts (ALK-Abello A/S, Horsholm, Denmark standard prick test, cow's milk). Histamine (10 mg/mL) was used as positive control and NaCl (0.9%) as negative control. The sensitivity of ≥3 mm compared to the negative control was considered allergen sensitivity.

Total IgE and Allergen-specific IgE Measurement

Total serum IgE, cow's milk sIgE measurement was done by ELISA method. Values above 0.35 kU/l were considered positive for sIgE.

Oral Food Challenge

The OFC was performed as an open challenge test after 2-4 weeks of elimination of the suspect food according to standard guidelines, except for children with a history of anaphylaxis.[2,4] Patients who received only breast milk were evaluated by provoking the mother after elimination. In the presence of objective findings such as exacerbation of atopic dermatitis, urticaria, angioedema, signs of airway obstruction (dyspnoea, rhonchi, wheezing, etc.), vomiting and anaphylaxis during the food challenge test, the test was considered positive and terminated. The patient, who could consume all steps without developing a reaction, was considered negative in the OFC and was followed up for 5-7 days in terms of late reactions. For cow's milk allergy, OFC was started with 0.1 mL diluted using pasteurized cow's milk or formula, according to the age of the patient, and continued with increasing doses every 15-30 minutes until 200 mL milk was reached or a reaction was recorded. Patients who did not show a reaction in the food challenge test were followed up in terms of late reactions and their reaction status was recorded.[2,4]

Statistical Analysis

The data were analysed using the SPSS 24.0 (Statistical Packages of Social Sciences) program on the computer. The conformity of the data to the normal distribution was evaluated with the Kolmogorov-Smirnov test; continuous variables were shown as mean±standard deviation and median, and categorical variables as frequency and percentage. Since age, total IgE and percentage eosinophil variables did not fit the normal distribution, non-parametric test (Mann-Whitney U test) was used for comparison and median values were compared. Chi-square test was used for the statistics of the obtained data. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 100 with CMPA were included in the study. The mean age of the patients was 10.8±10.21 months, and 49% (n=176) were male. 57% of the patients were followed up with IgE-mediated CMPA and 43% with FPIAP. There was a familial history of atopy in 23% (n=23) of the cases with CMPA. The most frequent symptoms were rush (51%, blood in stool (28%), cough (14%), and vomiting (10%).

No statistically significant difference was found between the gender distribution and mean age of the control group and the cases followed up with the diagnosis of CMPA (p>0.05) (Table 1). The male sex ratio in IgE-mediated CMPA cases was found to be significantly higher than the group followed up with the diagnosis of FPIAP (p=0.03) (Table 2). There was no statistically significant difference between the patients with CMPA and the control group in terms of the distribution of Aboriginal and Rh blood types (p>0.05). Additionally, there was no significant difference in blood type comparisons of the cases followed up with the diagnosis of IgE-mediated CMPA and FPIAP (p>0.05) (Table 2). The comparison of age, total IgE and eosinophil percentage values of IgE-mediated CMPA and FPIAP cases are given in Table 2. Age at diagnosis was found to be significantly higher in IgE-mediated CMPA cases compared to FPIAP cases (p<0.001) (Table 2). In the univariate logistic regression analysis, blood type distribution was not found to be a significant risk factor for the presence of CMPA (IgE-mediated CMPA and/or FPIAP) (p>0.05) (Table 3).

DISCUSSION

In this study, in which the relationship between Aboriginal and Rh blood types and CMPA was investigated, no significant difference was found between the blood types of the patients followed up with the diagnosis of CMPA and the blood types of healthy children. To date, blood types have been associated with many diseases such as cardiovascular diseases, cancers, autoimmune diseases, parasitic infections.[22] Additionally, various studies have found a relationship between blood types and allergic diseases such as atopic dermatitis, asthma, and allergic rhinitis. Falsarella et al.[11], in their study investigating the relationship between Aboriginal blood types and allergic rhinitis, reported that blood type O was associated with allergic rhinitis in men, but not in women. There are many studies supporting the relationship between allergic rhinitis and O blood type.[12-14]

Various results have been obtained in studies investigating the relationship between blood types and asthma. Kauffmann et al.[15] and Ronchetti et al.[16] showed that the frequency of asthma is higher in patients with non-secretory 0 blood type. Chen et al.[17] reported that there is a relationship between asthma and blood types in patients with secretory O blood type. Manisha and Yadav[18] showed a significant relationship in patients with O blood type, and Alo et al.[19] stated that there was a relationship between A blood type and asthma. However, there are also studies stating that there is no statistically significant difference between asthma and blood types.[23,24] In addition to asthma and allergic rhinitis, there are studies examining the relationship between atopic

Table 1. Distribution of gender and blood types according to patient and control groups, and comparison of mean/median age

	Patient (n=100)		Control (n=259)		Total	P*
	n	%	n	%	n	
Gender						0.484
Male	52	52.0	124	47.9	176	
Female	48	48.0	135	52.1	183	
Blood type						0.733
A	43	43.0	99	38.2	142	0.407
AB	7	7.0	26	10.0	33	0.372
B	13	13.0	38	14.7	51	0.684
O	37	37.0	96	37.1	133	0.991
Blood type						0.991
O	37	37.0	96	37.1	133	
Non-O	63	63.0	163	62.9	226	
Rh						0.634
Rh (-)	13	13.0	29	11.2	42	
Rh (+)	87	87.0	230	88.8	317	
	Mean±SD	Median [IQR]	Mean±SD	Median [IQR]		p**
Age (months)	10.89±10.4	9 [10]	10.76±10.17	9 [10]		0.939

*Chi-square test was used, **Mann-Whitney U test was used.
SD: Standard deviation, IQR: Interquartile range

Table 2. Gender and blood type distributions in the patient group according to the diagnosis types, and comparison of mean/median age, total IgE and % eosinophil values by diagnosis groups

	IgE-mediated CMPA (n=57)		FPIAP (n=43)		Total	p*
	n	%	n	%	n	
Gender						**0.03**
Male	35	61.4	17	39.5	52	
Female	22	38.6	26	60.5	48	
Blood type						0.307
A	27	47.4	16	37.2	43	0.31
AB	2	3.5	5	11.6	7	0.115
B	6	10.5	7	16.3	13	0.397
O	22	38.6	15	34.9	37	0.703
Blood type						0.703
O	22	38.6	15	34.9	37	
Non-O	35	61.4	28	65.1	63	
Rh						0.723
Rh (-)	8	14.0	5	11.6	13	
Rh (+)	49	86.0	38	88.4	87	
	Mean±SD	**Median [IQR]**	**Mean±SD**	**Median [IQR]**		**p****
Age (month)	14.61±13.45	10 [10]	5.83±3.6	5 [5]		**<0.001**
IgE total	243.22±252.74	139.25 [442.94]	15.19±21.3	10.63[13.64]		**<0.001**
% Eosinophil	4.61±3.02	4.4 [5.48]	5.15±4.16	3.9 [3.85]		0.745

*Chi-square test was used, **Mann-Whitney U test was used.

CMPA: Cow's milk protein allergy, FPIAP: Food protein-induced allergic proctocolitis, SD: Standard deviation, IQR: Interquartile range

Table 3. Logistic regression risk analyses according to blood types for the diagnosis of CMPA

	CMPA (IgE-mediated and FPIAP cases)					
	B	SE	Wald	p	OR	Lower-Upper (%95 CI)
A	0.198	0.239	0.687	0.407	1.219	0.763-1.948
B	-0.14	0.345	0.165	0.684	0.869	0.442-1.71
AB	-0.394	0.443	0.79	0.374	0.675	0.283-1.608
O	-0.003	0.244	0	0.991	0.997	0.618-1.608
Rh (+)	0.17	0.357	0.227	0.634	0.844	0.419-1.698

Univariate logistic regression analysis was used.

CMPA: Cow's milk protein allergy, FPIAP: Food protein-induced allergic proctocolitis, OR: Odds ratio, CI: Confidence interval

dermatitis and atopic diseases and blood type. Gangopadhyay et al.[20] reported in their study that B blood type was the most common in patients with atopic dermatitis, followed by A blood type, and 0 blood type was detected less frequently in the atopic dermatitis group than in the control group. In another study, it was reported that the most common blood type in patients with atopic dermatitis was B blood type and it was associated with the development of allergy.[21] Brachtel et al.[25] reported that blood types A and B are associated with atopic diseases such as rhinitis, asthma, and dermatitis.

In the study investigating the relationship between food allergies and blood types; Relationships have been reported between B and Rh negative blood types and IgE-mediated food allergies, and between 0, A, and Rh negative blood types and IgG-mediated food allergies.[26]

The prevalence of food allergy is higher in males.[4,27] Studies conducted in England and China have also reported that the frequency of food allergies is higher in males.[28,29] Similarly, Hikino et al.[30] also stated that male gender is a risk factor for food allergies and atopic dermatitis. Yavuz et al.[31] reported in their

study that IgE-mediated food allergies are more common in males. Elizur et al.[32] FPIAP, Katz et al.[33] stated that food protein-induced enterocolitis syndrome (FPIES) was more common in males. In our study, the ratio of males in the IgE-mediated group was found to be significantly higher than in the FPIAP group (p=0.03).

Study Limitations

We think that the limitation of our study is that the long-term prognosis is not followed to investigate the effect of blood types on the development of tolerance in patients with CMPA. As with other food allergies, several factors affect tolerance in CMPA. These; genetic predisposition, infections, changes in intestinal flora, age, frequency and amount of exposure, antigens passed through breast milk, mother's diet.[34] Since there are many factors affecting tolerance, we think that long-term studies are needed to investigate the tolerance relationship between blood types and CMPA.

CONCLUSION

In conclusion, to the best of our knowledge, this is the first study to investigate the relationship between the distribution of blood types in patients with CMPA and healthy subjects. To comprehend the role of blood type in the pathogenesis of CMPA and to investigate the effect of blood types on the development of tolerance in CMPA cases, we think that prospective studies with large groups are needed to evaluate clinical symptoms and more parameters.

Ethics

Ethics Committee Approval: Local ethics committee approval was obtained from Non-Invasive Clinical Research Ethics Committee of İstanbul Medipol University for the study (E-10840098-772.02-2630/21.01.2021, decision no: 84).

Informed Consent: Informed consent was acquired from the parents of all patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: H.T., H.T.N., Concept: F.N.A., H.T., Design: F.N.A., H.T., H.T.N., Data Collection or Processing: F.N.A., H.T., Analysis or Interpretation: F.N.A., H.T., H.T.N., Literature Search: F.N.A., H.T., H.T.N., Writing: F.N.A., H.T., H.T.N.

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Original Article

Can Vitamin B12 Deficiency Really Cause Vasovagal Syncope? Retrospective Analysis of 469 Pediatric Vasovagal Syncope Cases

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ABSTRACT

Objective: Syncope is a frequent reason for referral to pediatric cardiology clinics. Vitamin B12 deficiency is frequently diagnosed in pediatric patients. In this study, we determined the frequency of vitamin B12 deficiency in pediatric vasovagal syncope (VVS).

Methods: This study was designed retrospectively. VVS patients were identified from the hospital registry system with ICD code 'R55, syncope, and fainting'. The frequency of VVS and vitamin B12 levels of the patients were evaluated. Below 200 ng/L was considered vitamin B12 deficiency.

Results: Eight hundred twelve patients were identified with ICD code R55, syncope, and fainting' in pediatric cardiology hospital records. Two hundred sixteen patients were excluded from the study due to insufficient hospital records. Four hundred and sixty-nine patients were diagnosed with VVS. One hundred and seventy-three patients were excluded from the study because of non-available vitamin B12 level. Ninety-six patients had epileptic sezure/suspected VVS, 28 patients had psychogenic syncope and 3 patients had cardiac syncope. Demographic characteristics, hemoglobin and vitamin B12 levels, and the frequency of vitamin B12 deficiency were similar in the patient and control groups ($p>0.05$). Two hundred and sixty-four patients had normal vitamin B12 level, whereas 32 patients were diagnosed with vitamin B12 deficiency. Fifty-six patients who had normal vitamin B12 levels experienced frequent VVS and 6 patients with vitamin B12 deficiency experienced frequent VVS (21.2% vs 23.0%, $p>0.05$).

Conclusion: Although VVS can cause serious concern in patients and families, it is unlikely to be a serious underlying disease. Vitamin B12 deficiency was not found at a high rate in this disease as in other studies.

Keywords: Vasovagal syncope, transient loss of consciousness, vitamin B12 deficiency

INTRODUCTION

Vasovagal syncope is one of the most common reasons for pediatric cardiology outpatient clinics. It is classified under the subheading of reflex (neurally mediated) syncope in the guidelines.[1] Since its clinical features overlap with many fatal or non-fatal diseases, it causes serious concern both in the physician and in the family. While history taking and physical examination is often sufficient for diagnosis, further investigations may be required.

The main pathophysiology of VVS is a sudden decrease in cardiac output and a transient decrease in cerebral perfusion (vasodepression and/or cardioinhibition) with any trigger. As a result, transient loss of consciousness occurs (TLOC). TLOC is a transient condition characterized by loss of consciousness, abnormal motor control, loss of response, and short-term amnesia.[1] The sudden decrease in cardiac output is caused by hypotension due to insufficient vasoconstriction (vasodepression) or bradycardia/asystole due to parasympathetic dominance (cardioinhibition).[2] Triggering factors are orthostatic changes (such as standing up) or emotional factors such as fear, pain (somatic or visceral) or blood phobia.

Studies have shown that vitamin B12 deficiency causes neurological deficits.[3,4] Although the neurological function of vitamin B12

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is from different enzymes and pathways, the most important mechanism is thought to be impaired myelin formation and the relation between demyelinating diseases and B12 deficiency has been revealed.[5,6] However, it has not been proven that there is a deterioration in myelination in vitamin B12 deficiency.[7] Although vitamin B12 deficiency has been shown to be an etiological cause of VVS, studies have been conducted with few patients or comparing the head-up tilt test (HUTT).[8-10] The sensitivity of the HUTT is variable and insufficient, especially in VVS with emotional stimuli.[11-13]

VVS is a well-defined disease in clinical practice and most cases do not require further investigation. However, vitamin B12 level is frequently studied in routine practice and sometimes even if the level is normal, it is considered an etiological cause and replacement therapy is given.[8-10] However, for treating VVS, education and lifestyle modifications are sufficient to treat many patients, while additional medical treatments (B-blockers, alpha agonists, etc.) are required in few severe patients.[14]

To our knowledge, there is no study evaluating vitamin B12 deficiency in such a large case series in pediatric patients presenting with VVS. Vitamin B12 deficiency appears to be overdiagnosed in these patients, resulting in ignoring the education and lifestyle modifications that are most beneficial in the treating of the disease. In this study, we determined the frequency of vitamin B12 deficiency in VVS patients.

MATERIALS AND METHODS

The study was conducted retrospectively in the Kayseri City Hospital, Clinic of Pediatric Cardiology. The permission was obtained from the Clinical Research Ethics Committee of Kayseri City Hospital (decision no: 654, date: 16/06/2022).

The study was conducted with pediatric patients (8-18 years) referred to the pediatric cardiology clinic with syncope between October 2018 and October 2021 and a healthy control group. The patients were identified by searching the records of the pediatric cardiology outpatient clinic from the hospital registry system with the "ICD code R55, syncope, and fainting". The control group consisted of patients who were referred to the pediatric cardiology clinic with murmur, palpitation, or any other reason, whose transthoracic echocardiography (TTE) and electrocardiography (ECG) examinations were normal, and whose vitamin B12 levels were studied.

Patients who were referred to the pediatric cardiology clinic due to syncope and diagnosed with VVS according to the criteria of the European Society of Cardiology (ESC) (2018)[1] and who met the following criteria were included in the study as the patient group.

- Measuring the vitamin B12 levels in the pediatric cardiology clinic or the referral clinic,
- The VVS event had occurred within the last month.

Patients who met any following criterion were excluded from the study;

- Patients who could not be diagnosed with VVS at their first admission and who required further investigations such as HUTT and electroencephalography,
- Patients diagnosed with epileptic seizure, cardiogenic syncope, breath holding, psychogenic syncope,
- Patients with a head trauma history,
- Receiving B12 replacement therapy before the vitamin B12-level study [checked from patient history and ministry of health prescription registration system (e-prescription)],
- History of infection.

Vitamin B12 levels were measured by electrochemiluminescence immunoassay “ECLIA” in the hospital clinical laboratory on the same day and the intra-assay coefficient of variation (CVs) was 2.2%. Two hundred ng/L was accepted as cut-off value for deficiency.[3]

Each patient referred with syncope was evaluated with 12-lead ECG and TTE, and abnormalities were recorded. Patients with suspected arrhythmia were evaluated with 24-hour Holter ECG. The exercise stress test was applied to patients who experienced exercise-related syncope. Patients whose convulsion-VVS-psychogenic syncope distinction could not be made clearly were referred to another center for HUTT and were excluded from the study.

The patients were divided into 2 groups as those who had VVS attack only once and those who had recurrent attacks (2 or more).

Statistical Analysis

The normality of the distribution of vitamin B12 levels, demographic features were assessed with Kolmogorov-Smirnov test. Results are expressed as means for continuous variables and percentages for categorical variables. Continuous variables were compared between groups with Student’s t-test. The percentage of vitamin B12 deficiency and syncope frequency (one vs 2 or more) were analyzed with chi-square test. P-values <0.05 were considered significant. All statistical analyses were performed using the Statistical Package for the Social Sciences (ver. 22.0; SPSS Inc., Chicago, IL, USA).

RESULTS

During the past 3 years, 812 patients aged 8-18 years with ICD code "R55, syncope, and fainting" were identified in pediatric cardiology hospital records. Two hundred and sixteen patients were excluded from the study due to insufficient hospital records (Figure 1).

Twenty-eight patients were diagnosed with psychogenic syncope and 3 patients with cardiac syncope (long QT syndrome, catecholaminergic polymorphic ventricular tachycardia and coronary artery course anomaly). Ninety-six patients described epileptic seizures or suspected VVS. According to the ESC 2018 guideline, 469 patients were diagnosed with VVS (Figure 1).

Twenty-nine patients were evaluated with 24 h Holter ECG and 17 patients were evaluated with an exercise stress test. Cardiac syncope was not diagnosed with these tests.

Vitamin B12 levels and the frequency of vitamin B12 deficiency were similar in the patient and control groups (n=142) (10.8% vs 11.2%, Table 1).

The vitamin B12 level of 264 patients was normal, it was below 200 ng/L in 32 patients. One hundred and seventy-three VVS patients were excluded from the study (due to not evaluating vitamin B12 levels, receiving treatment, etc.). Fifty-six (21.2%) patients with normal vitamin B12 levels and 6 (23.0%) patients with low vitamin B12 levels experienced frequent (2 or more in the last 3 months) VVS (Figure 1). There was no statistical difference between the two groups (Table 2).

Following the diagnosis, patient education and lifestyle modification recommendations were made as the first therapy. Medical treatment was started at the time of diagnosis for 4 patients. Medical treatment was started for 12 patients because their complaints persisted despite education and lifestyle modifications. B-blockers were started as medical treatment, no other drug was needed in any patient.

Vitamin B12 replacement therapy was administered to 32 patients with vitamin B12 deficiency. However, only 6 of these patients complained of frequent VVS. These patients were not evaluated for the frequency of syncope as they also received other treatments.

DISCUSSION

In this study, we revealed that many patients were referred to the pediatric cardiology clinic with VVS, and vitamin B12 levels were frequently studied in the pediatric cardiology clinic or in the other centers, but vitamin B12 deficiency was not a common etiological cause in this disease as thought. VVS is a common disease in children and adolescents and causes serious anxiety in parents and patients. The similarity of the disease with epilepsy or other potentially fatal cardiac diseases in terms of clinical findings compels physicians to conduct further investigations.

In our clinic, in addition to the 12-lead ECG, as a routine practice, all patients are evaluated with TTE, although there is no murmur and no structural heart disease is suspected. If cardiac syncope is suspected, also 24-hour ambulatory Holter ECG examination can be performed. However, unnecessary tests do not reduce anxiety, in contrast, incidentally detected pathologies increase anxiety even more.

It has been shown that vitamin B12 deficiency causes different neurological findings.[3] However, histopathologically, myelination disorder could not be demonstrated in vitamin B12 deficiency.[7] It has been reported that vitamin B12 is low in VVS patients, but these studies were evaluated with a limited number of patients or according to the positive-negative HUTT.[8,15,16] However, the HUTT is recommended for the differential diagnosis of this disease only in suspicious cases, and the HUTT does not provide an idea about

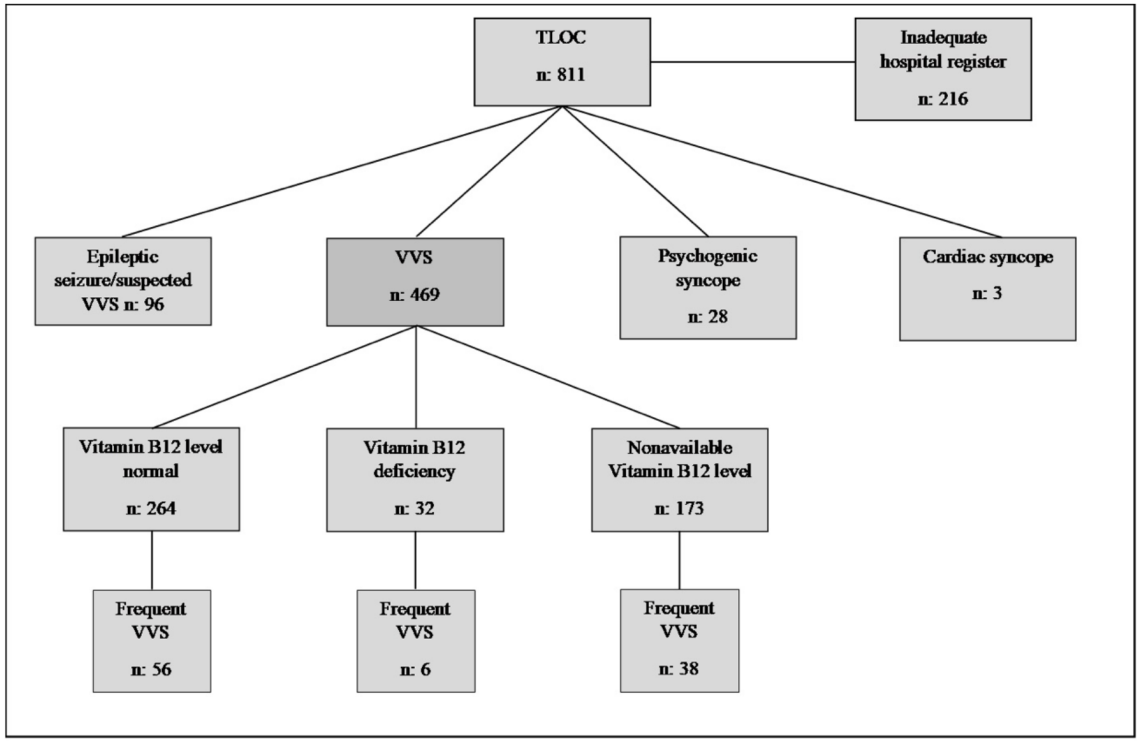

Figure 1. Number of patients referred with TLOC according to their diagnosis and vitamin B12 deficiencies

TLOC: Transient loss of consciousness, VVS: Vasovagal syncope, frequent VVS: 2 or more VVS in the last 3 months

Table 1. Demographic characteristics and vitamin B12 levels of the patient and control groups. Values are expressed as mean±SD, ratios and percentage

	Patient group (n=296)	Control group (n=142)	p-value
Body weight (kg)	36.4±12.3 (n=112)	42.7±9.8 (n=87)	0.487
Age (years)	13.3±4.2	15.7±6.3	0.128
Gender (Male/Female)	0.8	0.68	0.346
Hemoglobin (g/dL)	12.1±6.3	11.8±4.8	0.634
Vitamin B12 level (ng/L)	322.4±58.3	296.8±34.1	0.096
Vitamin B12 deficiency	32 (10.8%)	16 (11.2%)	0.854

SD: Standard deviation

Table 2. Demographic characteristics and vitamin B12 levels of patient groups. Values are expressed as mean±SD, ratios and percentage

	One syncope (last 3 months) (n=245)	Two or more syncope (last 3 months) (n=51)	p-value
Age (years)	31.5±3.6	41.1±9.3	0.078
Gender (Male/Female)	1.2	0.9	0.068
Hemoglobin (g/dL)	11.7±5.9	12.4±3.9	0.097
Vitamin B12 level (ng/L)	298.2±26.4	338.72±38.5	0.128
Vitamin B12 deficiency	26 (77%)	6 (23%)	0.517

SD: Standard deviation

the severity of the disease.[12,13,17] Additionally, cardioinhibition or vasodepression in VVS may occur not only with orthostatic changes but also with emotional triggers.[18,19] In our study, we did not find a relationship between vitamin B12 deficiency and VVS, as well as the diagnosis and severity of the disease. The neurological side effects of vitamin B12 may not be controversial, but its relationship with VVS may not be as obvious as be expected.

The prevalence of vitamin B12 deficiency differs significantly from country to country studies. The main reason for this difference may be socioeconomic status and different cut-off values. In Turkey, Varkal[20] reported this rate as 4.1% in a study evaluating 3115 children. Much higher prevalences have been reported in different countries, possibly due to low socio-economic status.[21,22] Although the B12 level was slightly higher in the control group, it was not statistically significant. In the study by Pektas et al.[8], 52.5% in the group with negative HUTT and 80% in the positive group. Our rates are far from the results.

A cut-off level of 100 ng/L, at which significant clinical findings occur, has been suggested for the vitamin B12 level.[3] However, there may be false positive or negative results. Therefore, homocysteine levels should also be checked in the evaluation of vitamin B12 levels. Additionally, considering that folic acid plays a role together with vitamin B12 in the remethylation of homocysteine, it would be more accurate to evaluate vitamin B12, folic acid, and homocysteine levels together.[3] Kovalchuk and Boyarchuk[9] evaluated 40 pediatric patients with a diagnosis of VVS and found that vitamin B12 levels were lower and homocysteine levels higher than the healthy control group. However, since our study was retrospective, we do not know the homocysteine levels. Folic acid levels were measured in very few patients and their levels were in the normal range. However, statistical analysis was not performed due to the small number.

The most valuable tool in the diagnosis of VVS is history taking from the patients and eyewitnesses of syncope. If the TLOC occurs with orthostatic changes or emotional stimuli (pain, fear, fear of blood, etc.) and consciousness quickly returns, further investigation is not required and the diagnosis is clear.

The recommended first-line therapy for treating VVS is education and lifestyle modifications. If known, it is recommended to stay away from the triggering factor (irritating smell, blood phobia etc.), and to sit or lie down when there are prodromal symptoms.[1] Increasing fluid and salt intake also reduces the recurrence of syncope.[23,24] In many patients, these measures are sufficient without medical treatment. If syncope recurrence is frequent, medical treatment is recommended. Parekh et al.[10] claimed that VVS patients with vitamin B12 deficiency and HUTT-positive VVS improved after vitamin B12 replacement and the HUTT became negative. However, the HUTT is not a good tool for evaluating the response to treatment.[25] In our series, few patients were treated with beta-blockers (metoprolol) and these patients benefited from medical therapy. The medical treatment of those whose symptoms decreased significantly for 1 year was discontinued. There are also patients who are given vitamin B12 replacement, but it is unclear whether these patients benefit from B12 replacement or from education and lifestyle modifications.

Study Limitations

The most important limitation was the retrospective design of our study. This is because hospital records may not be recorded properly. Although patients with insufficient records were excluded from the study, different physicians may not have paid enough attention to the disease and did not obtain sufficient and reliable patient histories. Vitamin B12 levels can be studied frequently by doctors and replacement therapy can be given. Although replacement therapy recipients are identified from the hospital registry and excluded from the study, there may be patients who are overlooked and these patients may affect the results. Since vitamin B12 and folic acid play a role in homocysteine remethylation, their levels may affect each other. Very few patients had folic acid levels and we did not perform statistical analysisIt would be best to evaluate VVS patients with vitamin B12, folic acid, and homocysteine levels in a prospective case-controlled study with a large number of cases.

CONCLUSION

Almost every patient experiencing syncope is referred to pediatric cardiology clinics. The concern of both the family and physician that there will be an underlying mortal disease leads to unnecessary tests. Of course, there are neurological manifestations of vitamin B12 deficiency. However, it does not seem to be an etiological cause as often as it is considered in a common disease such as VVS. VVS patients with vitamin B12 deficiency should be given replacement therapy. However, education, lifestyle modifications and medical treatments should not lag behind vitamin B12 replacement. Long-term prospective, case-controlled studies should be conducted to better understand the role of vitamin B12 in the pathophysiology of VVS.

Ethics

Ethics Committee Approval: The permission was obtained from the Clinical Research Ethics Committee of Kayseri City Hospital (decision no: 654, date: 16/06/2022).

Informed Consent: This study was designed retrospectively.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.S., M.A., Concept: S.S., M.A., Design: S.S., M.A., Data Collection or Processing: S.S., Analysis or Interpretation: S.S., Literature Search: S.S., Writing: S.S.

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Original Article

Etiological Factors of Opsoclonus Myoclonus Ataxia Syndrome: A Single Center Experience with Eight Children

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ABSTRACT

Objective: Opsoclonus myoclonus ataxia syndrome (OMAS) is a rare neurological disorder characterized by acute/subacute onset multi-directional chaotic eye movements, accompanied by myoclonus and cerebellar ataxia; as well as sleep disturbance, cognitive dysfunction, and behavioral disturbance can be observed.

Methods: We examined the information of eight patients (four females, four males) who applied to the hospital with OMAS between 2013 and 2020 from the medical records of the patients.

Results: The median age of onset of the initial symptoms was 17.5 months (8-30 months). The most common initial complaints were abnormal eye movement and gait unsteadiness, respectively. Paraneoplastic OMAS was observed in three patients (37.5%), whereas idiopathic and infection-related OMAS was detected in three, and two patients, respectively.

Conclusion: We emphasize that all symptoms of OMAS may not occur simultaneously, therefore comprehensive systemic investigations, and close observation should be made in patients with suspected OMAS.

Keywords: OMAS, opsoclonus, myoclonus, ataxia, neuroblastoma

INTRODUCTION

Opsoclonus myoclonus ataxia syndrome (OMAS), also known as dancing eye syndrome, is a rare neurological disorder, characterized by rapid, chaotic, and synchronous eye movements (opsoclonus), spontaneous muscle jerking (myoclonus), ataxia, and irritability.[1-3]

Ganglioneuroma/blastoma or neuroblastoma is detected in almost half of the pediatric OMAS patients; on the other side, the other half develops due to infections and idiopathic causes.[4,5] There is an autoinflammatory process in the background of this disease. Although no single pathogenic autoantibody has been identified in individuals with OMAS, increased B cell function and the presence of oligoclonal bands in cerebrospinal fluid (CSF)

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support the underlying autoimmunity and the importance of B cells in the pathophysiology of OMAS.[6,7]

Therefore, the recovery of neurological symptoms respond to immunotherapy. There are many treatment options as immunotherapy, including corticosteroids, adrenocorticotrophic hormone (ACTH), intravenous immunoglobulin (IVIG), cyclophosphamide, plasmapheresis, rituximab, and mycophenolate mofetil.[8-10]

In this report, we describe eight children with OMAS with different etiological factors and clinical presentations.

MATERIALS AND METHODS

Erciyes University Children's Hospital is a tertiary hospital in the city of Kayseri, in Central Anatolia, Turkey. This hospital is the sole pediatric referral center, serving a population of approximately 10 million, including the surrounding cities in the Cappadocia region. We reviewed the information of eight patients who applied to the hospital with the OMAS symptoms between 2013 and 2020 from the medical records retrospectively. Written informed consent was obtained from the parents of the included children. This study was approved by the Ethics Committee of Erciyes University, Faculty of Medicine (approval date: 06/01/2021, number: 2021/18).

RESULTS

We examined eight patients (4 females, 4 males) who presented with at least a symptom of OMAS (Table 1). The median age of onset of the initial symptoms was 17.5 months (8-30 months). The initial complaints of the patients were tremor, gait unsteadiness, myoclonic jerking, involuntary eye movements. The most common initial complaints were opsoclonus and gait unsteadiness (ataxia), respectively. Paraneoplastic OMAS was observed in three patients (37.5%), as idiopathic and infection-related OMAS was detected in the others. The median time from treatment to OMAS symptom remission was ten days (7-25 days) for seven patients. Opsoclonus symptoms continue in the high-risk neuroblastoma patient.

The first patient was admitted to the hospital at the age of 23 months with abnormal eye movements and gait unsteadiness. Although the neural structures were normal in the brain and spinal magnetic resonance images (MRI), a mass of 45x30x57 mm was detected in the posterior mediastinum (Figure 1). The tumor was totally resected, and he was diagnosed with ganglioneuroma. His complaints improved 14 days after the surgery and no additional treatment was required.

The second case was of a 16-month-old girl. She was admitted to the hospital with a complaint of involuntary eye movement. Neuron specific enolase (NSE) level, CSF examination, electroencephalography (EEG), brain and whole vertebral MRI, and abdominal ultrasonography (USG) were normal. She was followed up without any treatment because she had no additional complaints. When gait unsteadiness was noticed approximately eight months later, a solid tumor of 9.5x4.5x4 cm in size was detected in the left adrenal gland in the abdomen MRI (Figure 2). The tumor was completely resected by surgery, and its pathology was reported as a ganglioneuroblastoma. Since there were no tumor cells throughout the surgical margin and NSE was within normal limits, no needed additional chemotherapy. A single dose of IVIG was given only. Her complaints were improved ten days after the surgery.

At the age of 8 months of the patient three, a palpable mass was noticed in the abdomen. A paravertebral tumor and cranial metastases were detected on his MRI (Figure 3). The tumor was resected, and the pathology resulted in neuroblastoma. Metaiodobenzylguanidine scintigraphy revealed a left residual paravertebral mass, diffuse lymph node involvement in the abdomen, and metastasis in the brain. Therefore, she was considered a high-risk neuroblastoma according to the TPOG-NBL-2009 protocol. She was referred to our hospital for autologous harvest after receiving four courses of induction chemotherapy. The abnormal eye movement of the patient was noticed. Brain MRI was normal, no residual tumor was observed in abdominal MRI after four courses of chemotherapy. The opsoclonus was interpreted as a paraneoplastic. Autologous stem cell transplantation (ASCT) was performed, and the remaining chemotherapy was given. After the completion of planned chemotherapy, no residual tumors or metastasis were observed in the radiological imaging studies. The level of NSE level was within normal limits and the disease was considered complete remission. The complaint of opsoclonus did not ease. Therefore, IVIG was administered monthly for seven total doses for about a year, no change was observed. Currently, she is being followed up without any treatment for about two years.

Patients 4 and 5, one of them with gastroenteritis and the second one with upper respiratory tract infection were presented with abnormal eye movements. Any etiological factor could not be identified, but the viral infection was considered, symptoms resolved in about one week with the symptomatic treatments such as an antipyretic and empiric antibiotic. The etiology of OMAS could not be found in three patients all, only one patient received two doses of ACTH (75 U/kg/dose), and all patients' complaints improved in a short time.

NSE level, CSF examination, EEG, brain and whole vertebral MRI, abdominal USG, blood metabolic tests were performed for screening in all patients diagnosed with viral infection-associated or idiopathic OMAS. No etiological cause could be found. As the complaints of these patients regressed in a short time, no further evaluation was needed.

DISCUSSION

OMAS is a rare autoimmune neurological disorder with a median age of 18 months.[11] It is a clinical neurological syndrome characterized by opsoclonus, myoclonus, ataxia with or without behavioral abnormalities. This disease consists of involuntary eye movements, multifocal muscle jerks, and severe ataxia.[12] Opsoclonus is observed as involuntary eye movements in all directions, which could continue during asleep at 6-15 Hz. While

Table 1. The information of patients

Patients	Age at diagnosis (months), Gender	Initial symptoms	OMAS etiology	Abnormalities of EEG or MRI	First-line treatment	Time from treatment to OMAS symptom remission	Age at last follow-up, and neurologic status
Patient 1	23 mo, Male	Involuntary eye movements, Gait unsteadiness	Ganglioneuroma	EEG: Irregularity in ground rhythm, MRI: posterior mediastinal mass (45x30x57 mm)	Surgery	14 days	9 yo, Normal
Patient 2	24 mo, Female	Tremor, Gait unsteadiness, nystagmus	Ganglioneuroblastoma	MRI: Left surrenal mass (9.5x4.5x4 cm)	Surgery, IVIG (one dose)	10 days	8 yo, Normal
Patient 3	8 mo, Female	Involuntary eye movements	Neuroblastoma	MRI: paravertebral tumor and metastatic nasal cavity tumor	Surgery, ASCT, IVIG (7 doses)	Not resolved	3 yo, Opsoclonus continues
Patient 4	20 mo, Male	Involuntary eye movements	Viral infection	Normal	Observation, symptomatic, antibiotic treatment	9 days	6 yo, Normal
Patient 5	15 mo, Female	Involuntary eye movements	Viral infection	Normal	Observation, symptomatic treatment	7 days	5 yo, Normal
Patient 6	8 mo, Female	Abnormal eye movements	Idiopathic	Normal	Observation	10 days	4 yo, Normal
Patient 7	30 mo, Male	Gait unsteadiness, Myoclonic jerking	Idiopathic	Normal	ACTH (2 doses)	20 days	14 yo, Normal
Patient 8	13 mo, Male	Gait unsteadiness, Involuntary eye movements	Idiopathic	MRI: Myelination in bilateral periventricular white matter	Observation	25 days	5 yo, Normal

ACTH: Adrenocorticotrophic hormone, ASCT: Autologous stem cell transplantation, EEG: Electroencephalography, IVIG: Intravenous immunoglobulin, mo: Month-old, MRI: Magnetic resonance imaging, OMAS: Opsoclonus myoclonus ataxia syndrome, yo: Year-old

myoclonus is observed mainly in the form of irregular jerks in the body muscles, it makes children extremely difficult to walk with ataxic movements in the body and limbs. Diagnosis can be delayed since all classical features may not be presented initially. The median age of our patients' diagnosis was 17.5 months, and the most common complaints were opsoclonus and gait unsteadiness. Recently, neuropsychological disorders such as learning disability, language, and mental retardation in children with OMAS have been reported.[4] OMAS symptoms typically resolve with immunosuppressive therapy, although the recurrent course is common and long-term neuropsychological disorders persist in 80% of patients.[5,13]

Fortunately, only one patient still had neurological symptoms, probably because of the advanced stage neuroblastoma and late diagnosis. The rapid improvement of the neurological symptoms of the other two patients who have neuroblastic tumors can be attributed to the low-grade and the ability to cure with surgery alone. A series of six cases revealed that all neurological symptoms of patients diagnosed with OMAS due to neuroblastic tumor improved after treatment.[5] Another series of seven adult cases stated that the neurological symptoms of OMAS associated with coronavirus disease-2019 infection persisted despite the treatment in two patients.[14] Ben Achour et al.[12] reported that only three patients in a series of 15 children with OMAS still had neurological symptoms in about three-year follow-up. We think that our patients with non-paraneoplastic OMAS do not have permanent neurological symptoms due to their young age, early detection of symptoms and rapid response to treatment.

OMAS in children can be seen as a paraneoplastic syndrome and non-paraneoplastic syndrome (idiopathic, para-infectious). These

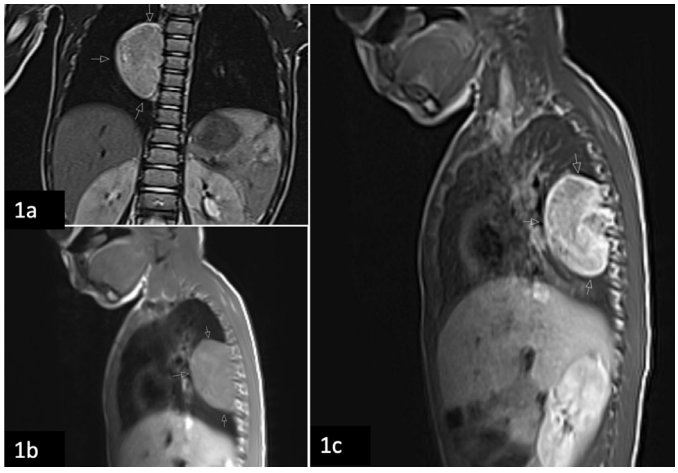

Figure 1. Posterior mediastinal right paravertebral ganglioglioma. (A) Coronal fat suppressed T2 weighted image and (B) sagittal T1 weighted image the tumor shows well defined margin and homogeny signal intensity, (C) post gadolinium T1W, sagittal plane: the tumor reveals relatively homogenous moderate enhancement pattern

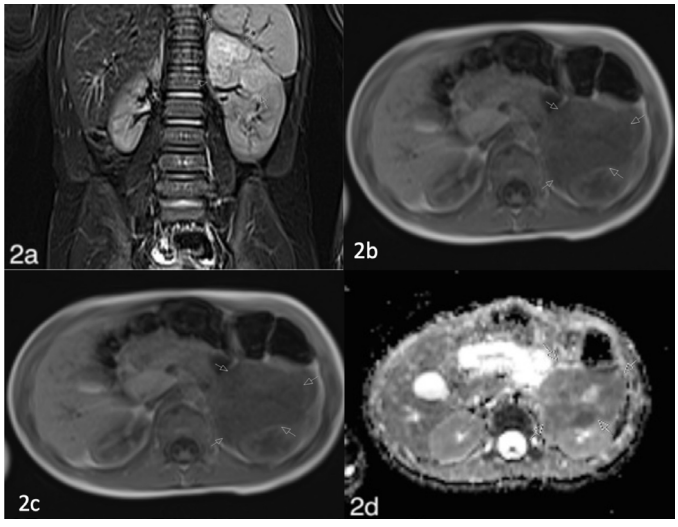

Figure 2. Patient 2, a 2-years-old female with left adrenal gland ganglioneuroblastoma. (A) coronal fat suppressed T2W hyperintense, (B) T1W hypointense homogenous signal intensity mass. The tumor infiltrating the left kidney, (C) diffusion-weighted image and (D) ADC map demonstrates restrictive diffusion (White arrows)

paraneoplastic and infectious associated opsoclonus/OMAS (IAO) are the most common causes in children; however, IAO is more dominant in adults. Neuroblastoma is seen as paraneoplastic in 50% of children, whereas small cell lung cancer and breast cancer are most common in adults. OMAS is accompanied by 1-2% of children with neuroblastoma. It is most seen in children under three years of age, the median age is 18 months.[13] The neuroblastoma that occurs with OMAS has an excellent oncologic outcome, is usually localized, insignificant, and differentiated. Complete

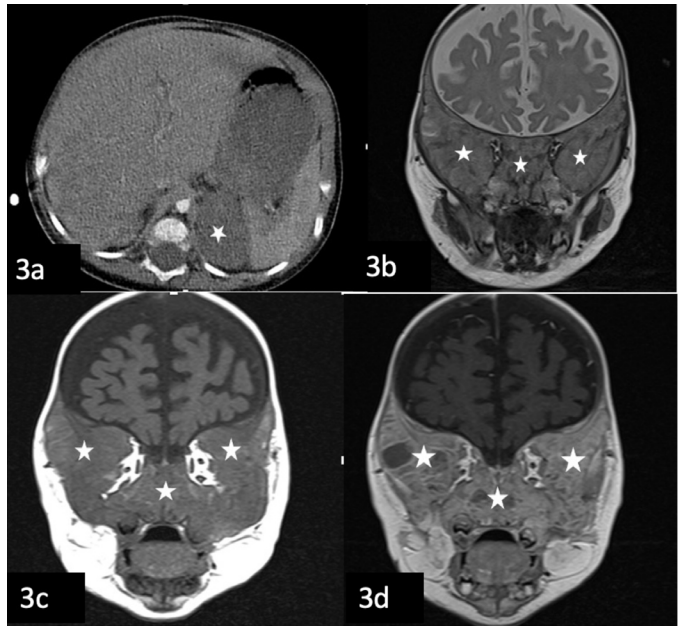

Figure 3. (A) Axial CT imaging shows smoothly contoured hypodense mass lesion in left surrenal gland localization. Coronal T2W (B) hyperintense, coronal T1W (C) hypointense and postcontrast images (D) show extensive metastatic bone lesions in the frontal bone, sphenoid bone, filling the nasal cavity, showing heterogeneous contrast enhancement

remission can be achieved only by surgery or sometimes with surgery plus standard chemotherapy. The association of high-risk neuroblastoma and OMAS is very rare.[15,16] Paraneoplastic OMAS developed in our three cases, the median age at diagnosis was 23 months. Although two of them had a tumor in the abdomen, the posterior mediastinal tumor was detected in the other. The two patients' diagnosis were ganglioneuroblastoma and ganglioneuroma, and complete remission could be achieved with only surgery. In our high-risk neuroblastoma patient, remission could be achieved with chemotherapy and ASCT in addition to surgery. But the neurological symptoms (opsoclonus) continues.

The second most common etiology of OMAS in children is infection. Viral infection is most common in IAO. Bacterial infections such as rickettsia, mycoplasma, salmonella, streptococcus, borreliosis, tuberculosis; fungal infections such as cryptococcosis and protozoal infections such as malaria were also reported to be the causes.[17,18] Among viruses, human immunodeficiency virus, influenza, mumps, herpes viruses, hepatitis C virus, arboviruses, and enteroviruses were identified.[19-21] In IAO patients, the agent could not be identified, but the symptoms of infection and OMAS improved with a symptomatic approach considering the viral infection.

Although the etiology of OMAS is still unknown; however, it is claimed as an underlying autoimmune mechanism. Considering the other family members of children who developed OMAS, it was observed that they are prone to autoimmunity compared to the control group.[22] Evidence shows that the abnormal immune-

mediated response targeting the central nervous system plays a vital role in the pathophysiology of OMAS, the cause of which is likely paraneoplastic or para-infectious.[6] Neuronal autoantibodies (anti-Hu, antineuronal, anti-neurofilament) were detected in the adults' serum and rarely in pediatric patients. Common surface-binding autoantibodies against the cerebellar structure and neuroblastoma cells have been identified.[23] One of them is Glutamate receptor δ2 autoantibody in the cerebellum.[24] Several inflammatory changes, such as increased IgG, IgM, and/or oligoclonal bands, may occur in the CSF of a patient with OMAS.

Furthermore, the demonstration of B cell activation in the CSF supports the autoimmune mechanism. In childhood OMAS, especially B-cell activating factor (BAFF) increase is observed. These levels decrease with immunotherapeutic treatment, such as steroids and ACTH.[6,7,16]

Because of the immune mechanism, immunomodulatory treatment, especially corticosteroid, has been the cornerstone of OMAS therapy. In the last 30 years, treatment regimens consisted of corticosteroids and ACTH. Many symptoms improved with this treatment regimen, but OMAS in children tend to continue for a long time with recurrence and behavioral disorders. Therefore, steroid therapy should be continued for a long time and may have serious side effects. Different treatment protocols have been used to prevent long-term use of steroids and to avoid side effects. In addition to this classical treatment, IVIG, rituximab, therapeutic plasma exchange, chemotherapeutic drugs such as methotrexate and cyclophosphamide have used.[2,25,26] Furthermore, the purpose of OMAS treatment is not only to reduce neurological symptoms but also to improve learning and behavioral skills. ACTH and steroids effectively reduce neurological symptoms in OMAS, whereas they are not sufficient in neuropsychological recovery and prevent relapse. IVIG is good at reducing neurological symptoms with a different mechanism of action, but it is insufficient to improve neuropsychological symptoms. Therefore, recent studies suggest that aggressive multiple aggressive therapies can improve outcomes in neuropsychological symptoms of OMAS.[27] In a study, the combination of pulse steroid, s IVIG, rituximab, and/or therapeutic plasma exchange was effective in both neurological and neuropsychological healing.[24,28,29] In other studies, immunotherapy with ACTH instead of steroids, combined with IVIG and rituximab has been found effective in terms of benefits and side effects.[30,31] Furthermore, cyclophosphamide added treatments reduced B-cell activity in CSF.[32] ASCT is increasingly used to treat autoimmune diseases. Transplantation has been reported in autoimmune diseases with neuroinflammatory factors such as chronic demyelinating polyneuropathy, multiple sclerosis, and myasthenia gravis. ASCT in autoimmune diseases removes pathogenic autoreactive cells and replace them with de novo repertoire immune cells.[33] We used two doses of ACTH in a patient with idiopathic OMAS, and the symptoms improved without the need for long-term use. Although the disease is in remission with surgery and ASCT in our patient diagnosed with high-risk neuroblastoma, neurological symptoms continue.

Study Limitations

Our study also has limitations. Firstly, no functional studies were performed in the included patients. Secondly, our patient cohort size was small. Larger cohorts will be needed to reveal the clinical spectrum of OMAS.

CONCLUSION

Neuroblastic tumors should be considered in all cases of OMAS in children. Early diagnosis and treatment of underlying diseases are essential to reduce complications and increase the chance of neurological recovery. We would also like to emphasize that all OMAS symptoms with different etiological factors may not occur at the same time; therefore, detailed evaluation and close observation should be made in patients with suspected OMAS.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of Erciyes University Faculty of Medicine (approval date 06/01/2021, number 2021/18).

Informed Consent: Written informed consent was obtained from the parents of the included children.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: V.G., H.S.D., H.G., M.K., A.K.B., H.P., Concept: V.G., E.Ü., H.P., Design: V.G., G.G., H.P., Data Collection or Processing: V.G., H.S.D., A.K.B., Analysis or Interpretation: V.G., E.Ü., H.G., H.P., Literature Search: V.G., M.K., Writing: V.G., A.K.B., H.P.

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Original Article

Management of Foreign Body Ingestion in Children: A Single-center Experience

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ABSTRACT

Objective: Foreign body (FB) ingestion is frequently encountered in childhood, and although the clinical results are often benign, it has high morbidity and mortality rates. Although guidelines for managing these children are available, there are still controversial aspects of the treatment recommendations. This study aimed to evaluate the treatment options for children who swallow FBs.

Methods: The study included 439 patients admitted with FB ingestion. Demographic and clinical features, type, size and localization of FB, treatment approach, and the timing of endoscopy were retrospectively scanned from hospital records.

Results: Most patients were male (58.3%) and 69.7% of the patients were aged <5 years. The most common symptom (42.3%) was nausea and vomiting and 82.5% of the patients were asymptomatic. The most common localization was the intestines (59.7%). While 84.1% of swallowed FBs came out with a spontaneous passage without complications, the endoscopic removal procedure was successful at the rate of 91.8%. The most frequently swallowed FB was coins (39.6%). Spontaneous elimination rates were higher for small coins and endoscopic removal rates were higher for large coins ($p<0.001$). The rate of emergency endoscopy was significantly higher in cases who swallowed a 2.6 cm coin ($p<0.001$). It was found that all sharp/pointed objects located in the intestine on admission came out spontaneously without complications. Sharp/pointed objects and button batteries located in areas accessible by esophagogastroduodenoscopy were more frequently removed using the endoscopic technique ($p<0.001$). In the cases with the ingestion of a single magnet or superabsorbent FB (giant growing toys), the FB came out with spontaneous passage without any adverse clinical outcome.

Conclusion: It can be suggested that this study of a large sample, showing the management of FBs without complications, will be of guidance in clarifying controversial aspects of the treatment.

Keywords: Foreign body ingestion, children, endoscopic removal, superabsorbent polymers

INTRODUCTION

Foreign body (FB) ingestion is one of the most common problems in childhood and usually occurs by accidental ingestion, starting from 6 months of age, when infants start exploring the objects around them by placing them in the mouth and this can continue up to 5 years of age.[1,2] The type of ingested FB may differ depending on social and sociocultural conditions.[3] Approximately 80-90% of ingested FB progress spontaneously in the gastrointestinal tract.[4] However, complications such as perforation, aortoenteric/enteroenteric fistula, and mediastinitis are important causes of morbidity and mortality and may develop depending on the type and localization of the FB.[5] Appropriate management can prevent complications and unnecessary invasive procedures. Although guidelines for managing these children are available, there are controversial suggestions regarding the treatment decision, and the experience and preference of the physician is also critical.[6] The decision to wait for the spontaneous passage of the swallowed FB or remove it endoscopically requires the evaluation of many

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conditions including the child's age, weight, presence of symptoms, and the characteristics of the swallowed FB.[4] Further reports must clarify the controversial issues regarding the treatment approaches. This study aimed to evaluate the choice of treatment approaches in children who have ingested foreign bodies.

MATERIALS AND METHODS

This single-centre, retrospective cohort study was conducted in the Clinic of Paediatric Gastroenterology, Necmettin Erbakan University Faculty of Medicine. The patients included were aged 0-18 years, and presented at hospital because of FB ingestion between 2019 and 2022. Patients were excluded from the study if they were not evaluated in the Paediatric Gastroenterology clinic, were treated in the otolaryngology or thoracic surgery clinics due to the localization of the object at the cricopharyngeal muscle level, had FB localization outside the gastrointestinal tract, or if the clinical/imaging findings were not available. No laxative or glucagon was used in any patient in the study group.

Age, gender, admission symptoms, type and size of the FB, radiological and endoscopic localization, type and duration of removal, the time from admission to esophagogastroduodenoscopy application were retrospectively scanned from the hospital records.

The swallowed FBs were classified into 7 groups including coins, batteries, magnets, sharp/pointed objects, deformable toys (balloon, play-dough), blunt objects that are not large/long and others (food bolus, large/long objects, superabsorbent objects). Endoscopy timing was classified as emergent, urgent, or elective according to the timing of endoscopy reported by The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN).[5] According to this classification, if esophagogastroduedonoscopy was applied after 2 h regardless of the fasting duration, it was defined as emergent, and if applied in the first 24 h after waiting for a period of fasting, it was defined as urgent. If esophagogastroduedonoscopy was applied after the first 24 h, it was defined as elective.

Ethical approval for the study was obtained from the Ethics Committee of Necmettin Erbakan University (decision number: 2022/3788). No informed consent was obtained due to the retrospective study design. The parents or primary caregivers approved the usage of the children's data for scientific research when they were admitted to the unit.

Statistical Analysis

Statistical analyses of the data were performed using SPSS 20.0 (IBM Inc, Chicago, IL, USA) program. Descriptive statistics were presented as frequency (percentage) for categorical data and mean ± standard deviation or median (interquartile range) for numerical data, as appropriate. Chi-square analysis with Monte Carlo correction was used to determine the relationships between categorical data. The Mann-Whitney U test and Kruskal-Wallis test were used to compare numerical data. When the differences were significant in multiple comparisons, critical difference pairwise comparison results were obtained. A value of $p<0.05$ was considered statistically significant.

RESULTS

Demographic Data

The study included 439 patients admitted to the hospital approximately 2019-2022 and diagnosed with FB ingestion. Most patients were male (58.3%) and 69.7% (n=306) were aged <5 years. The demographic characteristics, symptoms, ingested FBs and localizations of the FBs are shown in Table 1. The distribution of ingested FBs according to age groups are shown in Table 2.

Clinical Features

A direct radiograph was taken of all patients on admission. Of the foreign bodies, 388 (88.4%) were radiopaque and could be detected on direct radiography; 8 (15.7%) of the radiolucent FBs (n=51) could be localized endoscopically, 3 (5.9%) could not be

Table 1. Demographic and clinical characteristics

Characteristics	Categories	Mean ± SD
Age	Month	52.08±38.65
		n (%)
Gender	Male	256 (58.3)
	Female	183 (41.7)
Symptom	Asymptomatic	361 (82.2)
	Nousea/vomiting	33 (7.5)
	Difficulty swallowing/ salivation	19 (4.3)
	Abdominal pain	18 (4.1)
	Cough	5 (1.1)
	Respiratory distress	3 (0.7)
Foreign body	Coin	174 (39.6)
	Sharp/pointed object	68 (15.5)
	Battery	58 (13.2)
	Blunt object (not large/ long)	55 (12.5)
	Transformable toys	36 (8.2)
	Magnet	30 (6.8)
	Others*	18 (4.1)
Localization	Intestines	262 (59.7)
	Stomach	118 (26.9)
	Could not be localized	43 (9.8)
	Esophagus	12 (2.7)
	Duodenum	3 (0.7)
	Liver	1 (0.2)

*Others: Food impaction, superabsorbent object and large/long objects.
SD: Standard deviation

Table 2. Distribution of ingested foreign bodies according to age groups

	Age group n (%)				
Foreign body	**0-2 years**	**2-5 years**	**5-10 years**	**>10 years**	**p-value**
Coin	23 (23)	102 (49.5)	49 (47.1)		0.225
Sharp/pointed object	21 (21)	20 (9.7)	7 (6.7)	20 (69)	
Battery	23 (23)	28 (13.6)	4 (3.8)	3 (10.3)	
Blunt object (not large/long)	18 (18)	20 (9.7)	14 (13.5)	3 (10.3)	
Transformable toys	5 (5)	18 (8.7)	13 (12.5)		
Magnet	7 (7)	12 (5.8)	10 (9.6)	1 (3.4)	
Others	3 (3)	6 (2.9)	7 (6.7)	2 (6.9)	

The relation between the age groups and foreign object classifications was performed by chi-square test with Monte Carlo exact method

Table 3. Symptoms and endoscopy timing classification

Symptom	**Emergent n (%)**	**Urgent n (%)**	**Elective n (%)**	**Not performed n (%)**	**p-value**
Asymptomatic		16 (51.6)	22 (88)	323 (88.3)	<0.001*
Difficulty swallowing/salivation	11 (64.7)[a,b,c]	2 (6.5)[a]	1 (4)[b]	5 (1.4)[c]	
Nausea and vomiting	3 (17.6)	12 (38.7)[a,b]	1 (4)[a]	17 (4.6)[b]	
Abdominal pain	3 (17.6)	1 (3.2)	1 (4)	13 (3.6)	
Cough				5 (1.4)	
Respiratory distress				3 (0.8)	

*Significant at 0.05 level according to chi-square test.

[a,b,c]: Same superscript letters in each row denote the significant pairwise comparison of columns

detected with endoscopy, and remaining 78.4% did not undergo endoscopic intervention.

Esophagogastroduodenoscopy was performed in 73 (16.6%) patients. The FB could be removed in 67 (91.8%) patients with esophagogastroduodenoscopy, and could not be detected in 6 (8.2%) patients; these FBs were removed with spontaneous passage during follow-up. A total of 369 (84.1%) ingested foreign bodies were removed with spontaneous passage, 67 (15.3%) with esophagogastroduodenoscopy and 3 (0.7%) required surgical intervention (staples, a needle localized in the liver parenchyma, and penetrating multi-magnets). Esophagogastroduodenoscopy was performed in 17 patients (23.3%) emergently in 31 patients (42.5%) urgently, and in 25 patients (34.2%) electively. The timing of endoscopy differed significantly according to the localization of the FB. The time to endoscopy was significantly longer when the FB was detected in the stomach [median (Q1-Q3) 8 (6-58)], compared to esophageal localization [median (Q1-Q3) 1 (1-2)] (p<0.001). The time to endoscopy in asymptomatic cases [median (Q1-Q3) 11 (6-79,5)] was found to be significantly longer compared to symptomatic cases [median (Q1-Q3) 2 (1-7,25)] (p<0.001). The rates of elective endoscopy and spontaneous exit without endoscopy were higher in asymptomatic cases, whereas the emergent and urgent endoscopy rates were higher in symptomatic cases. In patients with symptoms of dysphagia/salivation and abdominal pain, endoscopy was performed immediately, while in those with symptoms of nausea/vomiting, the endoscopy was performed after a longer fasting period (p<0.001) (Table 3).

Ingested Foreign Body and Management

Coin

When the patients who ingested coins were evaluated it was found that the most frequently ingested coins were of 2.1 cm diameter (43.1%). The largest coin was 2.6 cm in diameter and was ingested by 12.6% of cases. The smallest coin was of 1.7 cm diameter and the patients who ingested these coins were mostly asymptomatic, whereas the patients who ingested the largest coins were found to be symptomatic (p=0.003). The rate of spontaneous passage was found to be higher for small coins, while the rate of endoscopic removal was higher for large coins (p<0.001). The rate of emergency endoscopy was significantly higher in cases who had swallowed a 2.6 cm coin (p<0.001) (Table 4). The patients with FB localized in the esophagus were symptomatic and emergency endoscopy was performed. In patients with FB localized in the stomach, only 1 (6.2%) FB was removed with spontaneous passage, and the remaining (93.8%) bodies did not progress during the follow-up period so were removed by elective endoscopy. All the coins with a diameter of 2.4 cm removed using the endoscopic technique, were localized in the stomach and were removed electively because they did not progress to the distal part of the stomach during clinical follow-up. Of the patients who swallowed a 2.1 cm diameter coin, 1 emergent (4-month-old infant who developed respiratory distress) and 1 urgent endoscopy (11-month-old infant, symptomatic) were performed.

Table 4. Comparison of the frequency, localization, symptoms, removal type, and the timing of endoscopy according to coin diameter

	Diameter					
	2.6 cm n (%)	**2.4 cm n (%)**	**2.1 cm n (%)**	**1.8 cm n (%)**	**1.7 cm n (%)**	**p-value**
Frequency	22 (12.6)	35 (20.1)	75 (43.1)	28 (16.1)	14 (8.1)	
Localization						
Esophagus	5(22.7)[a]		1 (1.3)[a]			<0.001*
Stomach	16(72.7)[a,b,c]	11 (31.4)[a]	19 (25.3)[b]	10 (35.7)	3 (21.4)[c]	
Intestines	1 (4.6)[a,b,c,d]	24 (68.6)[a]	55 (73.3)[b]	18 (64.3)[c]	11 (78.6)[d]	
Symptom						
Asymptomatic	15 (68.2)[a,b]	29 (82.9)	62 (82.7)	27 (96.4)[a]	14 (100)[b]	0.003*
Symptomatic	7 (31.8)[a]	6 (17.1)	13 (17.3)	1 (3.6)[a]		
Removal type						
Spontaneous	2 (9.1)[a,b,c,d]	30 (85.7)[a]	70 (93.4)[b]	27 (96.4)[c]	14 (100)[d]	<0.001*
Endoscopically	20 (90.9)[a,b,c]	5 (14.3)[a]	5 (6.6)[b]	1 (3.6)[c]		
Timing of endoscopy						
Emergent	5 (22.7)		1 (1.3)			<0.001*
Urgent			1 (1.3)			
Elective	15 (68.2)[a,b]	5 (14.3)	3 (4)[a]	1 (3.6)[b]		
Not performed	2 (9.1)[a,b,c,d]	30 (85.7)[a]	70 (93.4)[b]	27 (96.4)[c]	14 (100)[d]	

*Significant at 0.05 level according to chi-square test.

[a,b,c,d]: Same superscript letters in each row denote the significant pairwise comparison of columns

Table 5. The types and distribution of sharp pointed objects according to clinical charactreristics and treatment approach

	Foreign body						
	Pin	**Needle**	**Safety pin**	**Nail**	**Stapler**	**Toothpick**	**Other**
Frequency	27 (39.7)	3 (4.4)	10 (14.7)	19 (27.9)	2 (2.9)	3 (4.4)	4 (6)
Localization							
Esophagus						2 (66.7)	1 (25)
Stomach	4 (14.8)		4 (40)	2 (10.5)	2 (100)		
Duodenum	1 (3.7)					1 (33.3)	1 (25)
Intestines	22 (81.5)	2 (66.7)	6 (60)	17 (89.5)			1 (25)
Liver		1 (33.3)					
Not localized							1 (25)
Symptom							
Asymptomatic	21 (77.8)	2 (66.7)	10 (100)	18 (94.7)	2 (100)		1 (25)
Symptomatic	6 (22.2)	1 (33.3)		1 (5.3)		3 (100)	3 (75)
Removal type							
Spontaneous	22 (81.5)	2 (66.7)	6 (60)	18 (94.7)	1 (50)		2 (50)
Endoscopically	5 (18.5)		4 (40)	1 (5.3)		3 (100)	2 (50)
Surgery		1 (33.3)			1(50)		
Endoscopy timing							
Emergent	1 (3.7)					2 (66.7)	1 (25)
Urgent	4 (14.8)		5 (50)	1 (5.3)		1 (33.3)	2 (50)
Not performed	22 (81.5)	3 (100)	5 (50)	18 (94.7)	2 (100)		1 (25)

Others: Broken porcelain dish piece, drawing pin, clohtspin spring, dental laser tip

Table 6. Comparison of the frequency, localization, symptoms, removal type, and the timing of endoscopy according to battery diameters

	Size (diameter)					
	5 mm	**5-10 mm**	**10-15 mm**	**15-20 mm**	**20-25 mm**	**p-value**
Frequency	30 (53.6)	13 (23.2)	8 (14.3)	3 (5.4)	2 (3.6)	
Localization						
Esophagus			1 (12.5)			0.151
Stomach	8 (26.7)	4 (30.8)	4 (50)	1 (33.3)	2 (100)	
Intestines	22 (73.3)	9 (69.2)	3 (37.5)	2 (66.7)		
Symptom						
Asymptomatic	30 (100)[a,b]	10 (76.9)	3 (37.5)[a]	2 (66.7)[b]	2 (100)	0.013*
Symptomatic		3 (23.1)	5 (62.5)	1 (33.3)		
Removal type						
Spontaneous	30 (100)[a]	10 (76.9)[a]	3 (37.5)	2 (66.7)		<0.001*
Endoscopically		3 (23.1)[a,b]	5 (62.5)	1 (33.3)[a]	2 (100)[b]	
Endoscopy timing						
Emergent			3 (37.5)	1 (33.3)		<0.001*
Urgent		3 (23.1)[a,b]	2 (25)[c,d]		2 (100)[a,b,c,d]	
Not performed	30 (100)	10 (76.9)	3 (37.5)	2 (66.7)		

*Significant at 0.05 level according to chi-square test.

[a,b,c,d]: Same superscript letters in each row denote the significant pairwise comparison of columns

Sharp objects

When the types of sharp objects were compared no statistically significant differences were found in terms of symptoms, localization, exit pattern, and timing of endoscopy. However, in the patients with the FB localized in the intestine on admission, the FBs were removed through spontaneous passage without any intervention. Emergency or urgent endoscopy was performed in 17 patients (25%) (Table 5).

Button battery

When the patients who swallowed a button battery were examined, the most commonly ingested battery was 5 mm in size, in more than half of the patients (53.7%). There was no significant relationship between battery size and localization, but the rate of large diameter batteries removed by endoscopy was significantly higher ($p<0.001$). All 5 mm diameter batteries were removed through spontaneous passage. In 4 patients who had ingested 5-10 mm diameter batteries, the battery was localized in the stomach, and in 3 symptomatic patients, the battery was removed with urgent endoscopy. All the patients who ingested 10-15 mm and 15-20 mm batteries were symptomatic and the batteries were detected in the esophagus and stomach and were removed with endoscopy. Two patients who ingested a 20-25 mm battery were asymptomatic; the FBs were localized in the stomach and were removed with urgent endoscopy (Table 6).

Magnet

Of the 30 patients who ingested magnets, 4 (13.3%) had ingested multiple magnets and 26 had ingested a single magnet. All the magnets were <15 mm and in the patients with a single magnet it was removed spontaneously. In 2 patients who ingested multiple magnets, the FB was removed from the stomach with emergency endoscopy, in 2 patients the magnet was localized in the intestine and in one, it was surgically removed because the magnet was not removed spontaneously. There was no statistically significant difference in localization, removal pattern or removal times.

Food impaction

One of the 3 patients with food bolus was diagnosed with eosinophilic esophagitis after endoscopic removal of the food bolus localized in the esophagus. The other 2 were patients with a history of pyloric stenosis due to corrosive exposure, and the food bolus was removed endoscopically.

Superabsorbent foreign bodies

Superabsorbent foreign objects were those that could reach a maximum diameter of 10-20 mm when immersed in water. These were ingested by 13 (3%) patients and all were removed through spontaneous passage. Two patients who ingested a long FB (lollipop stick, pen) were asymptomatic; the FBs were removed from the stomach.

DISCUSSION

The results of this study showed that ingested FBs were frequently removed spontaneously without any problems, and the success of the endoscopy procedure was high.

Of the patients in this study, 69.7% were under the age of 5 and the rate of male gender was higher. These findings were parallel to the literature.[7,8] This young age has been associated with the inability of infants to distinguish edible objects and that they will put everything they hold into their mouths starting from the age of 6 months and it has been reported that gender was unimportant in this pathology.[9]

At the time of admission, 82.5% of the patients were asymptomatic. In symptomatic patients, the most common symptoms (42.3%) were nausea/vomiting. In previous studies, several conditions including vomiting, abdominal pain, and hypersalivation were reported as the most common symptoms.[10-12]

Direct radiography has been reported to be diagnostic in 64-96% of cases.[13] In this study, FB could be localized by direct radiography in 88.4% of the cases. The remaining cases had a history of swallowing a radiolucent FB. The NASPGHAN guidelines recommend endoscopic evaluation or the use of imaging methods such as computed tomography in cases of suspected radiolucent FB ingestion, if accompanied by clinical findings.[5] The current study patients who ingested radiolucent FBs and were asymptomatic were only followed up, and the FBs were subsequently removed with spontaneous passage without complications. Esophagogastroduodenoscopy was performed in all symptomatic cases. In this series, radiolucent FBs were removed endoscopically in only 8 cases (1.8%). Endoscopic evaluation can be recommended in symptomatic cases of radiolucent FB ingestion.

In this study, the intestines were the most common localization. In previous studies, different regions of the gastrointestinal tract, such as the esophagus and intestine have been reported to be the most common localization.[7,8,14,15] This variability may be due to different characteristics of the patients and the ingested object. In this study, FBs were followed up in 84.1% of the cases, according to the "wait-observe" method and the objects were removed spontaneously without complications. In patients who underwent endoscopy, the success of the procedure was 91.8%. In the remaining patients, the FB could not be removed endoscopically because it had progressed to the distal of the duodenum, and during follow-up, it was removed with spontaneous passage. In the literature, the success of endoscopic procedures varies ranging between 31.1% reported by Diaconescu et al.[13] and 98% reported by Pokharel et al.[16]

In this study, urgent esophagogastroduodenoscopy was determined to be most frequently performed and the timing of endoscopy differed significantly according to the localization of the FB and the presence of symptoms. The time to endoscopy was significantly longer when the FB was localized in the stomach compared to the esophagus. Similarly, the time to endoscopy in asymptomatic cases was significantly longer than in symptomatic cases. Additionally, spontaneous removal and elective endoscopy rates were higher in asymptomatic cases, while emergent and urgent endoscopy rates were higher in symptomatic cases. NASPGHAN recommends emergency endoscopy in patients with FBs located in the esophagus and in any localization if the patient is symptomatic.[5] The current study findings are consistent with these recommendations.

Consistent with the literature, the most frequently ingested FB in this study was coin (39.6%).[11-13] The type of ingested FB may vary according to sociocultural differences. In some studies conducted in Turkey 10 years ago, different results were seen. Yalçin et al.[3], examined 112 cases of FB ingestion and reported that the most frequently swallowed FB was safety pin. Aydoğdu et al.[8] reported that safety pins were swallowed more frequently by infants, and that pins were swallowed more frequently by girls older than 10 years, and this was due to cultural and belief differences. Dereci et al.[7], reported that the most frequently ingested FB was a coin. Gezer et al.[17] also reported that a coin was the most frequently ingested FB in a case series of 1,000 children who had swallowed FBs. There can be considered as several reasons for this change. Rather than pinning good luck charms of blue beads to the clothes of infants nowadays they tend to be pinned to their beds. Additionally, magnets produced for attaching headscarves have replaced pins recently.

In a study evaluating children who swallowed coins over 10 years, Chen et al.[18] reported that of 252,338 children admitted to the emergency service with the complaint of ingesting coins, 20 died. The risk varies according to patient characteristics and the size of the coin. In Turkey, coin sizes vary between 1.7-2.6 cm. The most commonly ingested coin in the current study was 50 kurus (2.1 cm). The patients who ingested small coins were more often asymptomatic and most of the coins were removed with spontaneous passage. Patients who ingested large diameter coins were more symptomatic and the rate of endoscopic removal was higher. All coins localized in the esophagus with a diameter of 2.6 cm were removed by emergency endoscopy. In a 23-month-old infant who swallowed 1 TL (2.6 cm), endoscopy could not be performed because the coin was localized in the intestine on admission, and was removed with spontaneous passage. However, NASPGHAN recommends performing endoscopy in children, due to the low probability of a FB larger than 2.5 cm being able to pass through the pylorus.[5] If a large diameter coin has passed the pylorus and cannot be reached using the endoscopic technique in children, the "wait-observe" approach with close follow-up for the surgical requirement seems to be an inevitable practice in centres where enteroscopy cannot be performed.

The "wait-observe" approach was performed for all coins of 2.4 cm diameter (n=11) that were localized in the stomach on admission. However, the coins of 2.4 cm diameter could not pass the pylorus in 5 of 11 patients and were removed by elective endoscopic technique. Since the diameter of 50 kurus is 2.4 cm, which is very close to the 2.5 cm limit in terms of the possibility of spontaneous passage, it can be suggested that the "wait-observe"

approach should be applied in the same way as for patients who ingested 1 TL.

In this study, the second most frequently swallowed FB was sharp/pointed objects. In the literature, it has been reported that most sharp/pointed FBs are removed spontaneously without any complications and those that cannot be removed spontaneously most commonly got stuck in the upper esophageal lumen.[19,20] In this study, it was determined that sharp/pointed objects were eliminated spontaneously without any problems if they were in the intestine, and those localized in areas accessible by esophagogastroduodenoscope were largely removed endoscopically. NASPGHAN recommends endoscopic removal of esophageal sharp/pointed FBs, and removal of those that have advanced to the stomach in asymptomatic cases, if the object does not progress after 3 days of follow-up.[5] However, in the current study population, endoscopic removal was often preferred when sharp/pointed objects were located in areas that could be reached by esophagogastroduodenoscopy. The reason why our practices differ from the recommendations in the guidelines and literature is that especially since sharp/pointed objects cause more anxiety in families and they cannot take the risks that may develop if the object is not removed spontaneously and therefore, they prefer endoscopic removal.

Button batteries are among the most worrisome ingested FBs due to the risk of morbidity and mortality reported recently.[21] In this study, more than half of the patients swallowed a 5 mm size button battery and all of these batteries were spontaneously removed. In most patients, button battery of 5 mm diameter was localized in the intestine on admission. All the patients with a 5 mm diameter button battery in the stomach were asymptomatic. In these patients, elective endoscopic removal was planned following the fasting period, but the procedure was not performed because the object was seen to be localized in the intestines on direct X-ray performed just before the endoscopy. The rate of endoscopic removal was found to be significantly higher in large diameter batteries. It was determined that all button batteries larger than 10 mm located in the esophagus and stomach were removed endoscopically. In one patient the battery was localized in the esophagus and it was removed by emergency endoscopy. It has been accepted that button batteries localized in the esophagus indicate emergent endoscopic intervention, but the approach to batteries in the stomach is controversial. Contrary to previous recommendations, NASPGHAN has recommended that gastric button batteries should be removed by endoscopy and follow-up should be considered only in the presence of criteria including small battery, a short time since swallowing, older and asymptomatic patients. Even under these conditions, NASPGHAN left the decision of endoscopy to the expert opinion in terms of evaluating the possibility of esophageal damage.[5] In a case series by Leinwand et al.[21], it was reported that in one patient who swallowed button battery, elective endoscopy was planned to remove the button battery localized in the stomach and patient died from major artery injury. In this study, all button batteries larger than 10 mm that were accessible by esophagogastroduodenoscopy were removed endoscopically without complications. There is clear information for emergent endoscopic removal of esophageal button battery. However, gastric button batteries remain a matter of debate. Considering this extensive case series all of which were resolved without complications, it can be recommended that after a period of fasting if the battery remains in the stomach and has not advanced radiographically, endoscopy should be planned regardless of size and the battery should be removed.

In the study, it was found that 6.8% of the patients swallowed magnets. Abbas et al.[22] reported an alarming 8.5-fold increase in magnet swallowing cases in the United States. In studies conducted in Turkey, the frequency of ingesting magnet has been low enough to cause these cases to be classified as "other".[3,14,17] In this study, the reason for the high incidence of magnet ingestion is the same as the decrease in needle ingestion cases. This study was conducted in the region where the wearing of headscarves and many headscarf-related accessories are most common in Turkey. Recently, magnets have been produced to be used instead of pins to fix the headscarf, and these are quite common in this region. This has reduced needle ingestion, but introduced a new risk of magnet ingestion. It was determined that all ingested magnets were smaller than 15 mm, and 86.7% of the patients ingested a single magnet and the magnets were removed spontaneously. Endoscopic removal was performed in 6.6% of patients who ingested multiple magnets and the magnets were localized in the stomach. In the remaining patients, the magnet was localized in the intestines and only 1 patient-required surgery. These results were consistent with the NASPGHAN guideline recommendations.[5] It can be suggested that magnets should be removed endoscopically when they are located in areas that can be reached by esophagogastroduodenoscopy.

Food impaction is rarer in children than in the adult population. In the cases reported in literature, the impaction is frequently located in the esophagus and are secondary to pathologies such as eosinophilic esophagitis and achalasia.[23] In this study, food impaction was located in the esophagus in 1 case with eosinophilic esophagitis. In 2 cases, pyloric stenosis developed due to corrosive substance ingestion, and gastric food impaction was detected. To the best of our knowledge, these are the first gastric food impaction cases reported in the literature.

Superabsorbent polymers are beads of various sizes that can enlarge when immersed in water. Since there are few case reports stating that they expand after swallowing and cause obstruction in the gastrointestinal tract and there is no study reporting otherwise, NASPGHAN recommends endoscopy in the presence of suspected ingestion and if the foreign object cannot be detected with endoscopy, follow-up for signs of ileus is recommended.[5] Case series reported after the publication of the guideline have reported better results. Mehmetoğlu[24] and Cairns et al.[25] reported that none of the patients who ingested superabsorbent polymers required intervention or surgery. In this study, endoscopy was performed in only 1 of the 13 patients as the time between ingestion and admission was short although the

object was found to have progressed. In the other 12 patients, the beads were ingested after they had been kept in water for a long time, and the diameter after enlargement was <20 mm. None of the 12 patients developed signs of intestinal obstruction. It can be suggested that since these objects with slippery surface progress rapidly, the probability of detecting these objects with endoscopy is low, especially in patients admitted long after the ingestion. If possible, evaluation of the size after soaking may be helpful in patient management.

Study Limitations

Important limitations of this study were that it was a retrospective and single-center study. Since the type and frequency of swallowed objects may show regional differences, it is impossible to generalize the results to the national level. Nevertheless, the sample size can be considered large enough to evaluate the treatment approaches to FBs that are frequently ingested in our region.

CONCLUSION

In this large sample, it was seen that ingested FBs are frequently removed spontaneously, large-scale coins do not proceed with the "wait-observe" method and require elective endoscopy, endoscopic removal is often preferred when sharp/pointed objects and button batteries are located in areas that can be reached by esophagogastroduodenoscopy, and superabsorbent polymers are removed spontaneously. These results were similar to the findings of other recent studies. To clarify the controversial aspects in the current guidelines for treating children who have ingested FBs, and to evaluate treatment options, there is need for further prospective studies.

Ethics

Ethics Committee Approval: Ethical approval for the study was obtained from the Ethics Committee of Necmettin Erbakan University (decision number: 2022/3788).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.Y., Ö.Y., Concept: A.Y., Ö.Y., Design: A.Y., Ö.Y., Data Collection or Processing: A.Y., Ö.Y., Analysis or Interpretation: A.Y., Literature Search: A.Y., Ö.Y., Writing: A.Y.

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Original Article

Investigation of Etiology, Treatment Outcomes and Risk Factors of Epilepsy in Down Syndrome

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ABSTRACT

Objective: Although epilepsy does not appear in the classic definitions of Down syndrome (DS), the prevalence of epilepsy is higher in these cases than in the general population. The purpose of this retrospective study was to evaluate the demographic, neuroradiological, and electrophysiological characteristics, and responses to treatment of patients with DS undergoing epileptic seizure.

Methods: Karyotype analysis, time of onset of seizures, types of seizure, electroencephalography (EEG) characteristic, antiepileptic drug used, and comorbidity were considered during evaluation. EEG and magnetic resonance imaging at the time of first admission were assessed during patient evaluation.

Results: Patients with DS (n=43) were enrolled in this study. Twenty-three of them were subjects with epilepsy. Seventeen (73.9%) of the 23 patients were boys and six (26.1%) were girls. The mean age of the patients was 21.7 months (standard deviation ± 4.8), and mean age at onset of seizures was 12.6 months. Comorbidity other than epilepsy was present in 13 (56.5%) patients. The most common seizure type, in 14 cases (60.9%), was focal seizures, four of which involved epilepsy developing following stroke secondary to cardiac surgery. Hypothyroidism was observed in all six patients with epileptic spasm. Only four of 20 patients without epilepsy have non-neurologic comorbidities.

Conclusion: This study may support the knowledge regarding the relationship between hypothyroidism and epilepsy in DS. Non-neurologic comorbidities are a significant risk factor for epilepsy in DS.

Keywords: Childhood, Down syndrome, epilepsy, epileptic spasm, hypothyroidism

INTRODUCTION

Down syndrome (DS) is the most common chromosomal disorder worldwide, affecting all races and genders. Most cases occur due to trisomy 21 through a non-disjunction mechanism. More rarely, it may be seen with balanced translocations or mosaicism. The reported prevalence in the USA is 12.6/10,000.[1] Children with DS have higher rates of heart disease, celiac disease, hypothyroidism, and epileptic disorders than the general population. Epilepsy is seen in 1.6-23.1% of children with DS, higher than general population.[2-10] Epilepsy in DS shows a bimodal distrubation, first in infancy and the second peak in the 6th decade.[11] The prevalence of epileptic spasm in these patients varies from study to study, from 6.7% to 66.7%.[3-12] Frequently seen predisposing factors are birth asphyxia, complex cardiac anomalies, history of major cardiac surgery, and stroke.

The first aim of this retrospective study was to evaluate the demographic, neuroradiological, and electrophysiological characteristics, and responses to treatment of patients with DS undergoing epileptic seizure. The second aim is to raise awareness in primary care physicians and podiatrists.

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MATERIALS AND METHODS

Seventy-two cases of DS presenting to our hospital for various reasons in 2019-2021 were included in the retrospective cross-sectional study. Twenty-three patients with histories of epilepsy and with resolved or new-onset epileptic seizures were investigated. Karyotype analysis, time of onset of seizures, types of seizure, electroencephalography (EEG) characteristics, antiepileptic drugs used, and comorbidities were considered during evaluation. The clinical, magnetic resonance, and electroencephalographic findings of patients diagnosed in our hospital were retrieved from the children's hospital records. The tests of cases with histories of epilepsy and treated in another center but followed up in our hospital were obtained from the data in the patients' possession. EEG and magnetic resonance imaging (MRI) at the time of first admission were assessed during patient evaluation. Patients with incomplete tests or who could not be contacted were excluded from the study.

Intractable epilepsy was defined as at least two seizures a month despite consecutive or concurrent use of two or more antiepileptics at appropriate dosages and durations.

The developmental status of the patients was evaluated by "Layton's Developmental Scale for Children with DS" until 72 months of age. After 72nd month gross motor function classification system was used.

Statistical Analysis

Data were processed through SPSS version 22.0. Quantitative variables were expressed as mean ± standard deviation (SD), and median range (maximum-minimum). Frequencies and percentages were calculated for all categorical characteristics. Chi-square analysis was used to compare dependent and independent variables. To compare the mean values, it was planned to use the Student t-test. Statistical significance was set at $p<0.05$.

The approval of the ethics committee has been obtained from Tekirdağ Namık Kemal University Non Invasive Clinical Research Ethics Committee (approval no: 2021.239.10.03, date: 26.10.2021).

RESULTS

Patients with DS (n=43) were enrolled in this study. Twenty-three of them were subjects with epilepsy. The patients' demographic, clinical, and laboratory findings are summarized in Tables 1 and 2.

In the epilepsy group, 17 (73.9%) of the 23 patients were boys and six (26.1%) were girls. The mean age of the patients were 21.7 months (minimum one, maximum 80, SD±4.8), and mean age at onset of seizures was 11.5 months. Comorbidity other than epilepsy was present in 14 (60.8%) patients. Four patients had undergone cardiac surgery, three for complete atrioventricular septal defect repair, and one for ventricular septal defect repair. The most common seizure type, in 14 cases (60.9%), was focal seizures, four of which involved epilepsy developing following stroke secondary to cardiac surgery. Seizures in five of the six patients with epileptic spasm ceased with adrenocorticotropic hormone (ACTH) therapy, while seizures in the other case were resistant, and vigabatrin therapy was added to treatment.

In the non-epileptic group, the mean age was 20.5 months (±2.5). Only four of 20 patients without epilepsy have non-neurologic comorbidities. One has cardiac malformation, 2 have hypothyroidism and one has celiac disease. In subjects with epilepsy, non-neurologic comorbidities were clearly increased and statistically significant ($p=0.01$).

DISCUSSION

Although epilepsy does not appear in the classic definitions of DS, the prevalence of epilepsy is higher in these cases than in the general population.[11-13] While focal seizures are generally seen, epileptic spasm is also observed at a higher rate than in the general population.[6-8] Although the seizure etiology varies, the most common factors are cardiovascular surgeries, previous infections, and structural cerebral abnormalities.[8] All comorbidities were more common in the group with epilepsy compared to the group without epilepsy ($p<0.01$). This finding reveals that the comorbidities are clearly the risk factor for developing epilepsy in DS.

The pathophysiology of epileptic spasms are still insufficiently understood. However, inhibitor and neurotransmitter imbalance has generally been implicated.[14] A difference in cortical laminar structures, and synaptic length and density has also been reported in children with DS compared to normal children, and seizures may cause a result.[15] Decreased oligodendrocyte myelination and differentiation and changes in action potential are also seen, and it has been suggested that these findings can result in intellectual disability and seizures in DS.[15]

Focal seizures were observed in six of the eight cases with cardiac anomalies in our patient group, generalized seizure in one, and epileptic spasm in one. One striking finding was the presence of hypothyroidism in all six children with epileptic spasms. This finding reveals that hypothyroidism may be a risk factor for epilepsy in patients with DS. Thyroid hormones play an essential role in the fetal brain development and physiological processes. Uncorrected hypothyroidism may cause epilepsy by effecting inhibitory neurotransmitters and inducing oxygen radicals.[16] The developmental stages of children without DS with congenital hypothyroidism determined at neonatal screening may be delayed compared to control group stages.[17] Even in case of regular L-thyroxine therapy in DS cases with early hypothyroidism, seizures are likely due to neuronal development being affected.

No such study considers antiepileptic drug tolerability and effectiveness in DS. Common rules for antiepileptic usage in childhood is valid in these patients. However, the comorbidites-like hypothyroidism or aggressive behavior- should always keep in mind. Generally, carbamazepine and levetiracetam in focal seizures, ACTH in epileptic spasms and valproate in myoclonic

Table 1. Comparison of demographic characteristics and laboratory findings of Down syndrome cases with and without epilepsy history

	Subjects with epileptic spasm	Subjects with other seizure types	Total (n=23)	Subjects without seizures (n=20)	p-value
Age (month)					
Mean (SD)	8.3 (±3.8)	22.6 (±4.61)	21.7 (±4.8)	20.5 (±2.5)	0.09
Gender					
Male n (%)	5 (21.7)	12 (52.2)	17 (73.9)	13 (65)	0.08
Female n (%)	1 (4.3)	5 (21.7)	6 (26.1)	7 (35)	0.1
Seizure onset					
<12 months n (%)	1 (4.3)	12 (52.1)	13 (56.5)	-	-
12 months-60 month n (%)	5 (21.7)	4 (17.3)	9 (39.1)	-	-
>60 months n (%)	-	1 (4.3)	1 (4.3)	-	-
Seizure onset (month)					
Mean (SD)	11 (±1.8)	13.2 (±2.81)	12.6 (±2.1)	-	-
Seizure type					
Epileptic spasm n (%)	6 (26.1)	-	6 (26.1)	-	-
Focal n (%)	-	14 (60)	14 (60.8)	-	-
Generalized n (%)	-	3 (13)	3 (13)	-	-
Electroencephalography					
Hypsarrhythmia n (%)	6 (26.1)	-	6 (26.1)	-	-
Focal epileptic activity n (%)	-	9 (39.1)	9 (39.1)	-	-
Generalized epileptic activity n (%)	-	3 (13)	3 (13)	-	-
Focal slow wave activity n (%)	-	5 (21.7)	5 (21.7)	-	-
Antiepileptic drug response at onset					
First drug n (%)	5 (21.7)	12 (52.1)	17 (73.9)	-	-
Add-on therapy n (%)	1 (4.3)	3 (13)	4 (17.3)	-	-
Intractable epilepsy n (%)	-	2 (8.6)	2 (8.6)	-	-
Magnetic resonance imaging					
Post-stroke gliosis n (%)	-	4 (17.3)	4 (17.3)	-	-
Cerebral atrophy and gliosis n (%)	1 (4.3)	2 (8.6)	3 (13)	-	-
Non-specific gliosis n (%)	1 (4.3)	4 (17.3)	5 (21.7)	-	-
Normal n (%)	4 (17.3)	7 (30.4)	11 (47.8)	-	-
Antiepileptic drug at last visit					
Monotherapy n (%)	6 (26.1)	7 (30.4)	13 (56.5)	-	-
Polytherapy n (%)	-	3 (13)	3 (13)	-	-
None n (%)	-	8 (34.7)	8 (34.7)	-	-
Non-neurologic co-morbidity					
Cardiopathy + hypothyroidism n (%)	1 (4.3)	2 (8.6)	3 (13)	-	-
Cardiopathy n (%)	-	5 (21.7)	5 (21.7)	1 (15)	0.01
Hypothyroidism n (%)	5 (21.7)	-	5 (21.7)	2 (15)	0.01
Chronic respiratory insufficiency n (%)	-	1 (4.3)	1 (4.3)	-	-
Celiac disease n (%)	-	-	-	1 (5)	
None n (%)	-	9 (39.1)	9 (39.1)	16 (65)	0.04
Total non-neurologic complications n (%)	6 (26)	8 (60.9)	14 (60.9)	4 (35)	0.01

SD: Standard deviation

Table 2. Demographics and clinical characteristics of all patients with epilepsy

Patients	Age (months)	Gender	Seizure onset (months)	Seizure type	EEG (initial)	MRI	AED response	Up-to-date AEDs	Comorbidity	Developmental status
1	12	Male	6	ES	Hypsarrhythmia	Normal	Partial response to ACTH, Vigabatrin added on.	The LEV	AVSD, Hypothyroidism	Had cardiac surgery, walks with aid, severe intellectual disability
2	18	Male	13	Focal	FEA	Post-stroke gliosis	Full response to the LEV.	None	VSD	Right hemiplegia walks independently, moderate intellectual disability
3	11	Female	5	Generalized	GEA	Normal	Full response to VPA.	None	None	Moderate intellectual disability
4	16	Male	12	ES	Hypsarrhythmia	Normal	Full response to ACTH.	The LEV	Hypothyroidism, ASD	Severe intellectual disability
5	12	Male	8	Generalized	GEA	Cerebral atrophy and gliosis	Partial response to the LEV.	LEV, CMZ	VSD	Spastic diplegia, cannot walk independently, mild intellectual disability
6	18	Female	12	ES	Hypsarrhythmia	Normal	Full response to ACTH.	The LEV	Hypothyroidism	Severe intellectual disability
7	15	Male	12	Focal	FEA	Post-stroke gliosis	Full response to CMZ.	CMZ	AVSD	Had cardiac surgery, right hemiplegia, walks with aid, mild intellectual disability
8	10	Male	5	Focal	FEA	Cerebral atrophy and gliosis	Partial response to the LEV.	The LEV, VPA, CMZ	ASD	Spastic tethraplegia, cannot walk, cortical blindness, mild intellectual disability
9	80	Male	72	Focal	Focal slowing	Normal	Full response to the LEV.	None	Hypothyroidism, ASD	Moderate intellectual disability
10	24	Female	18	Focal	FEA	Normal	Full response to PB.	None	VSD	Autism spectrum disorder, severe intellectual disability
11	12	Female	2	Focal	Focal slowing	Post-stroke gliosis	Partial response to the LEV.	The LEV, CMZ, CLB	VSD	Had cardiac surgery, right hemiplegia occurs and walk independently, mild intellectual disability
12	16	Male	13	ES	Hypsarrhythmia	Normal	Full response to ACTH.	The LEV	Hypothyroidism	Severe intellectual disability

Table 2. Demographics and clinical characteristics of all patients with epilepsy

Patients	Age (months)	Gender	Seizure onset (months)	Seizure type	EEG (initial)	MRI	AED response	Up-to-date AEDs	Comorbidity	Developmental status
13	11	Male	4	Focal	Focal slowing	Non-spesific gliosis	Full response to PB.	None	None	Mild intellectual disability
14	7	Male	5	Generalized	GEA	Normal	Full response to VPA.	None	None	Moderate intellectual disability
15	5	Male	2	Focal	Focal slowing	Non-spesific gliosis	Full response to the LEV.	The LEV	None	Mild intellectual disability
16	18	Male	12	ES	Hypsarrhythmia	Non-spesific gliosis	Full response to ACTH.	The LEV	Hypothyroidism	Severe mental retardation
17	10	Female	4	Focal	FEA	Post-stroke gliosis	Partial response to the LEV.	CMZ	AVSD, Chronic respiratory insufficiency	Had cardiac surgery, bedridden, trakeostomia, lower extremity spasticity, dependent to home-type mechanical ventilator, severe intellectual disability
18	12	Male	8	Focal	FEA	Non-spesific gliosis	Full response to the LEV.	The LEV	None	Moderate intellectual disability
19	15	Male	12	Focal	FEA	Normal	Full response to the LEV.	None	None	Moderate intellectual disability
20	12	Male	10	Focal	Focal slowing	Normal	Full response to the LEV.	The LEV	None	Mild intellectual disability
21	18	Male	11	ES	Hypsarrhythmia	Cerebral atrophy and gliosis	Full response to ACTH.	The LEV	Hypothyroidism	Severe intellectual disability and spastic tethraplegia
22	17	Male	10	Focal	FEA	Normal	Full response to the LEV.	None	None	Moderate intellectual disability
23	22	Female	10	Focal	FEA	Non-spesific gliosis	Partial response to CMZ.	The LEV	None	Moderate intellectual disability

ES: Epileptic spasms, EEG: Electroencephalography, FEA: Focal epileptic activity, GEA: Generalized epileptic activity, ACTH: Adrenocorticotropic hormone, the LEV: Levetiracetam, CMZ: Carbamazepine, CLB: Clobazam, VPA: Valproic acid, PB: Phenobarbital, AVSD: Atrioventricular septal defect, ASD: Atrial septal defect, VSD: Ventricular septal defect, AED: Antiepileptic drug, MRI: Magnetic resonance imaging

seizures should be the first choices.

Seizure control was achieved in 17 patients with the initial treatment initiated, while seizures were intractable in the remaining patients, and these patients used multiple antiepileptic therapies. Seizure control was established with intramuscular synthetic ACTH therapy in five of the six cases with epileptic spasms. The addition of vigabatrin being required in only one case. Previous studies have reported that epileptic spasm in cases of DS responds well to ACTH therapy.[8,9,18,19] One study even reported a response rate to ACTH of 98%.[20] Consistent with the previous literature, an ACTH response of approximately 83% was observed in cases with epileptic spasm-type seizures. However, other studies have suggested the exact opposite.[20,21] Nabbout et al.[22] reported five patients with DS diagnosed with infantile spasms. In this report epileptic spasms were stopped after short-term treatment with vigabatrin without any side effects. We attribute this literatural inconsistency to patient group heterogeneity and to differences in EEG interpretation. Cases with comorbidities such as cardiopathy and hypothyroidism were also included in our report.

Cardiac anomalies are observed at higher rates in cases with DS than in the general community and have been described as a risk factor for epileptic spasm in some studies.[19] In contrast to this hypothesis, cardiac anomalies were detected in only one of the six patients with epileptic spasms in this study. Patients with longer cardio-pulmonary bypass, aortic clamp times and deep hypothermic circulatory arrest also counted as risk factors for epilepsy after major cardiac surgery. Furthermore, extracorporeal membrane oxygenation use and longer hospital stays are also risk factors for stroke and post-cardiac operation epilepsy.[23]

Specific EEG pathologies were not seen, similar to previous studies.[11] Only the specific findings or commonly seen for the particular epileptic syndromes were revealed, such as hypsarrhytmia in epileptic spasms and focal discharges after post-stroke epilepsy.

Myoclonic seizures were not observed in the patient group. Comorbid late-onset myoclonic seizures and Alzheimer disease have been reported in cases of DS.[24] The absence of myoclonic seizures in the patient group may be because myoclonic seizures are usually seen in adults.

Developmental tests were applied to all patients. Before 72nd month "Layton's Developmental Scale for Children with DS" until 72 months of age.[25] After 72nd month gross motor function classification system was used. Mental problems were detected in all patients in spectrum from mild to severe intellectual disability. All patients without motor deficit have normal or non-spesific gliotic areas on the brain MRI. We can say that brain MRI can be predictive of motor deficits in the follow-up. All patients have some degree of intellectual disability as DS. All six patients with the history of infantile spasms have severe mental retardation in up-to-date examinations. This finding shows us the association between epilepsy type and intellectual functioning in this patient group.

Study Limitations

The current study had some limitations. First, the retrospective design may lead to the risk of bias. Second, the study was conducted in a single center with small sample size. However, the current study is one of the few studies, regarding the coexistence of DS and epilepsy, which was a rare condition. Studies are needed with a larger sample size of patients with DS and epilepsy.

CONCLUSION

This study may support the knowledge regarding the relationship between hypothyroidism and epilepsy in DS. Non-neurologic comorbidities are a significant risk factor for epilepsy in DS. Epilepsy in DS is not rare and should always be kept in mind by families, pediatricians, and family physicians.

Ethics

Ethics Committee Approval: The approval of the ethics committee has been obtained from Tekirdağ Namık Kemal University Non Invasive Clinical Research Ethics Committee (approval no: 2021.239.10.03).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: G.G., N.S., Concept: G.G., N.S., Design: G.G., N.S., Data Collection or Processing: G.G., Analysis or Interpretation: G.G., Literature Search: G.G., Writing: G.G., N.S.

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Original Article

Monitoring of Antibody Levels Following SARS-CoV-2 Infection in Children and Late Adolescents with Inflammatory Rheumatic Diseases

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ABSTRACT

Objective: We monitored the severe acute respiratory syndrome-coronavirus-2 antibody levels in patients with inflammatory rheumatic diseases (IRD) and healthy children.

Methods: Healthy children and patients under 21 who were initially seropositive, were included in the study. Antibody levels of all subjects were measured again after the third and sixth months by the ELISA method. In this process, their symptoms were also questioned in terms of coronavirus disease-2019.

Results: The study included 35 participants (female/male: 1.69) (healthy control group: 10, patient group not receiving biological therapy: 19, patient group receiving biological therapy: 6). Their mean age was 14.27±5.49 years. Of the participants, 13 (37.1%) had a history of symptomatic infection, and 4 (11.4%) had a history of hospitalization. At the end of the six-month, a significant decrease was found in the immunoglobulin G levels of the participants (p=0.002). While no significant decrease was observed in the first trimester (p=0.085), there was a sharp decrease in the second trimester (p<0.001). Age, sex, presence of IRD and use of biological agents did not affect this decrease.

Conclusion: Although they decrease rapidly in the second trimester, we showed that antibodies acquired by infection in healthy children and children with IRD mostly stay at an acceptable level after six months. These data can be used to schedule vaccination programs. Besides, we showed that IRD and biological drugs do not affect the decrease in antibody levels. Therefore, no additional precautions may be required regarding vaccination in this patient group.

Keywords: Pediatrics, rheumatology, SARS-CoV-2, antibodies, viral

INTRODUCTION

Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) is responsible for the current pandemic. This novel virus causes a disease, which might be highly fatal named coronavirus disease-2019 (COVID-19). Although highly effective and safe vaccines against the virus are currently available, SARS-CoV-2 is still a major health concern worldwide.[1]

It was previously reported that increased age, male gender, and comorbidities such as cardiovascular diseases, diabetes, and hypertension are the main risk factors for poor outcomes.[2,3]

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Luckily, COVID-19 is often much milder in children than in adults.[4-6] Although a life-threatening condition named multisystem inflammatory syndrome in children was described in April 2020, it is an extremely rare complication of the virus.[7]

Due to conflicting data, it remains unclear whether individuals with inflammatory rheumatic diseases (IRD) are at increased risk of severe COVID-19.[8-11] However, it was recently reported in a large cohort that there is a significantly increased risk of both hospitalization and symptomatic infection in children with IRD.[12]

Another conundrum regarding the children with IRD during the pandemic was their active immunization after the SARS-CoV-2 infection. They were considered they may not be able to generate and sustain sufficient humoral immune response due to their immune-disturbed conditions caused by both their diseases and medication.[13] In this study, we primarily monitored the anti-SARS-CoV-2 immunoglobulin (Ig) G levels acquired by natural infection of seropositive children with and without IRD for six months. Secondary aim was to evaluate the clinical and demographic variables that may affect the decreasing pattern of the antibodies.

MATERIALS AND METHODS

Study Design

We conducted a prospective study. Those who were seropositive by measuring anti-SARS-CoV-2 IgA and IgG antibodies were included in the study regardless of the reason for their serological examination. Antibody levels of these seropositive subjects were measured again twice, 90 days and 180 days after the first measurement. Variables that may affect the lowering trend of the antibody levels with timing were evaluated. The study was started in July 2020, and the last antibody measuring test was performed in June 2021. We finished the study before August 2021, when children in our country were allowed to be vaccinated for the first time. Therefore, none of our subjects had been vaccinated against SARS-CoV-2.

Participants

In one of our previous works, which evaluated asymptomatic seropositivity, participants who were found to be seropositive by measuring anti-SARS-CoV-2 IgA or IgG antibodies were included in the study.[14] Additionally, those found to be seropositive by measuring antibodies 14-30 days after the contact history or COVID-19 suggestive symptoms had been started were also included. Patients diagnosed with any IRD before the age of 18 years and currently under 21 and healthy individuals under 18 years are included in the study. The children with IRD whose follow-up period was less than six months were excluded. During the intervals between the antibody measurements, COVID-19 suggestive symptoms were checked for each patient, and those with symptomatic infection or contact history were excluded from the study due to the possibility of affecting the results.

Children previously admitted to our center due to a non-specific and transient complaint before the pandemic and without any diagnosed underlying disease were established as the healthy control group. The patients with IRD who did not receive any biological treatment were called the non-biologic group, and the patients with IRD who were currently under biological treatment for at least six months at the first serologic evaluation time were called the biological group. Patients whose biological treatments were stopped during the antibody monitoring period were excluded from the study.

Antibody Measuring

The sera of the patients were removed from each subject's venous blood sample by centrifugation at 4.500 rpm and stored at -20 °C until testing. IgA and IgG detection against SARS-CoV-2 spike protein was assayed by the ELISA method using test kits based on the sandwich and semi-quantitative principles (EUROIMMUN AG, Lübeck, Germany). According to the manufacturer's instructions, assays were carried out with a dilution ratio of 1:100. Microplates were read at 450 nm (reference 620-650 nm) wavelength by an automated microplate reader (BioTek ELx800, Istanbul, Turkey). Then, absorbance (optical density, OD) was calculated for all samples.

Antibody ratios of samples were calculated by dividing the sample's OD by Calibrator's OD. While the ratios higher than 1.1 were classified as positive, those lower than 0.8 were classified as negative. Subjects with borderline ratios between 0.8 and 1.1 were classified as negative or positive based on the expert microbiologist's opinion.

Ethical Approval

The study protocol was approved by the Institutional Ethics Committee of İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine (approval number: 04/16/20–29430533-604.01-01-54959). The recommendations of the Declaration of Helsinki for biomedical research involving human subjects were followed in this study. We obtained informed consent from the participants and their parents.

Statistical Analysis

We performed the statistical analysis using IBM SPSS Statistics for Windows, Version 22.0 (Armonk, NY: IBM Corp). The chi-square test or Fisher's exact test was used to compare the categorical variables, expressed as numbers (percentages). Kolmogorov-Smirnov test was used to assess the distribution of continuous variables. While those with a normal distribution were presented as mean ± standard deviation, those distributed abnormally were presented as median (minimum-maximum). Mann-Whitney U test or Student's t-test was used to compare the continuous variables when appropriate.

Repeated measures ANOVA was performed to assess the changing pattern of antibody levels of participants over time. A multivariate ANOVA test was performed to interpret the effects of variables such as age, gender, existing IRD, and receiving treatments on the lowering trend of antibody levels of the participants. Statistical

significance was defined as $p<0.05$. Prism software (Prism 8, GraphPad Software, San Diego, California) was used to graph data.

RESULTS

Baseline Characteristics of All Study Populations

Overall, 35 subjects (female/male: 1.69) were eligible for the study. Their mean age was 14.27±5.49 years. While there is not any underlying disease in ten (28.6%) subjects, nine (25.7%) had juvenile idiopathic arthritis (JIA), eight (22.9%) had Familial Mediterranean Fever (FMF), five (14.3%) had systemic lupus erythematosus (SLE), one (2.9%) had cryopyrin-associated periodic syndrome (CAPS), one (2.9%) had a deficiency of adenosine deaminase 2 (DADA2), and one (2.9%) subject had Sjögren's disease.

Six patients (17.1%) received biological disease-modifying anti-rheumatic drugs (bDMARDs) (adalimumab: 3, canakinumab: 2, etanercept: 1). Four of six (66.6%) had a contact history, and two patients (33.3%) (one with oligoarticular JIA and under adalimumab treatment, and the other one with systemic JIA under canakinumab treatment) who both had a contact history, had a history of symptomatic SARS-CoV-2 infection. However, none of them were hospitalized.

While eleven (31.4%) patients were under colchicine treatment, four (11.4%) patients were receiving steroids. During the whole study, ten (28.6%) were received at least one type of conventional disease-modifying anti-rheumatic drug (cDMARDs) (hydroxychloroquine: 8, methotrexate: 3, mycophenolate mofetil: 1, azathioprine: 1). Five of ten patients (50%) under cDMARD treatment had a contact history, and three of five had a history of symptomatic SARS-CoV-2 infection. All but one patient with symptomatic infection had a contact history, as well. Although two of them required hospitalization, both recovered completely.

Thirteen (37.1%) subjects (JIA: 5, FMF: 4, healthy children: 2, SLE: 1, Sjögren's disease: 1) (female: 61.5%) had a history of symptomatic SARS-CoV-2 infection. The most common symptom was fatigue, which was seen in nine (25.7%) subjects. The other symptoms were cough (n=7, 20%), sore throat (n=7, 20%), myalgia (n=7, 20%), rhinorrhea (n=6, 17.1%), diarrhea (n=5, 14.3%), fever (n=4, 11.4%), dyspnea (n=4, 11.4%), abdominal pain (n=4, 11.4%), rash (n=3, 8.6%), and vomiting (n=1, 2.9%), respectively.

Four (11.4%) patients were hospitalized. All were females. Patient 1 was 12.2 years old and was diagnosed with JIA. She was not receiving any medication. Patient 2 was 13.3 years old, diagnosed with Sjögren's disease and was receiving methotrexate and hydroxychloroquine. Patient 3 was 18.9 years old, diagnosed with SLE and was receiving hydroxychloroquine. Patients 4 was 19.7 years old, diagnosed with FMF and was under colchicine treatment. All but one with JIA had a contact history.

While twenty-two subjects (62.9%) had an asymptomatic infection, nine participants (25.7%) had mild-to-moderate COVID-19 disease course. Additionally, four patients (11.4%) who required hospitalization were considered to have a severe SARS-CoV-2 infection. Since those stating suspicious symptoms for COVID-19 or contact history were excluded during the study as we mentioned before, none of the included subjects were considered to have re-infection. In symptomatic cases, there was a 22.15±3.71 day-period between the first antibody measurement and the onset of COVID-19 symptoms. In asymptomatic but with contact history cases, the interval between the first serological evaluation and exposure date was 20.5±2.87 days. However, it was impossible to identify this period in incidental cases.

While the median IgA ratio of the patients was 1.55 (0.54-8.59), the mean IgG ratio was 3.56±2.67 on day 0. The mean IgG ratios on day 90 and day 180 were 2.92±2.08 and 1.98±1.33, respectively.

Comparisons Between the Groups

Those without underlying diseases were called the healthy control group (n=10). Among those with IRD (n=25), while those receiving bDMARDs (n=6) were called the biological group, the rest (n=19) were called the non-biologic group.

The median ages of the healthy control group, the biological group, and the non-biologic group were 9.55 (2.21-19.35), 17.49 (8.39-20.64), and 17.41 (3.90-20.80) years old, respectively. The participants of the healthy control group were significantly younger than the other group ($p=0.014$). There were no significant differences between the groups concerning antibody levels, and the frequencies of female gender, contact history, symptomatic SARS-CoV-2 infection, and hospitalization due to COVID-19 (Table 1).

Antibody Monitoring Data

While there was no significant difference between the IgG ratios on day 0 and day 90 ($p=0.085$), a significant decrease was observed from day 90 to day 180 ($p<0.001$). In total, the IgG ratios were significantly decreased from day 0 to day 180 ($p=0.002$) (Table 2). The IgG ratios of the participants for each group on day 0, day 90, and day 180 are available in Figure 1. Age, gender, the presence of IRD, receiving treatments such as steroids, colchicine, bDMARDs, and cDMARDs, contact history with a known infected case, symptomatic SARS-CoV-2 infection history, and hospitalization history due to COVID-19 were not found to be effective in the decreasing trend of IgG ratios of the subjects. The detailed data are given in Table 3.

Eight participants (22.9%) converted to seronegative at the end of the study: a nine-year old healthy boy, three patients with FMF under colchicine, a twenty-year old female with JIA under remission, an eight-year old boy with JIA receiving methotrexate, a twenty-year old female with SLE under hydroxychloroquine, and a nineteen-year old boy with JIA receiving adalimumab.

DISCUSSION

Anti-SARS-CoV-2 IgG levels of thirty-five seropositive children and late adolescents (healthy children: 10, those with IRD under

Table 1. Baseline characteristics of the subjects				
	Healthy control group (n=10)	**Non-biologic group (n=19)**	**Biologic group (n=6)**	**p-value**
Age [median (min-max)]	9.55 (2.21-19.35)	17.49 (8.39-20.64)	17.41 (3.90-20.80)	**0.014**
Female gender (n, %)	7 (70%)	11 (57.9%)	4 (66.7%)	0.892
Diagnosis				
FMF (n, %)	-	8 (42%)	-	
JIA (n, %)	-	5 (26.5%)	4 (66%)	
SLE (n, %)	-	5 (26.5%)	-	
CAPS (n, %)	-	-	1 (17%)	
DADA2 (n, %)	-	-	1 (17%)	
Sjögren (n, %)	-	1 (5%)	-	
Ongoing treatment				
Steroid (n, %)	-	2 (10.5%)	2 (33.3%)	
Colchicine (n, %)	-	10 (52.6%)	1 (16.7%)	
c-DMARD (n, %)	-	9 (47.4%)	1 (16.7%)	
Methotrexate (n)	-	2	1	
Mycophenolate mofetil (n)	-	1	-	
Hydroxychloroquine (n)	-	8	-	
Azathioprine (n)	-	1	-	
b-DMARD (n, %)	-	-	6 (100%)	
Adalimumab (n)	-	-	3	
Canakinumab (n)	-	-	2	
Etanercept (n)	-	-	1	
Contact history (n, %)	4 (40%)	10 (52.6%)	4 (66.7%)	0.665
Symptomatic infection (n, %)	2 (20%)	9 (47.4%)	2 (33.3%)	0.365
Symptoms				
Cough (n)	1	4	2	
Rhinorrhoea (n)	-	4	2	
Headache (n)	-	5	2	
Fatigue (n)	1	6	2	
Myalgia (n)	-	6	1	
Abdominal pain (n)	-	2	2	
Nausea-Vomiting (n)	-	1	-	
Diarrhea (n)	1	4	-	
Rash (n)	1	2	-	
Fever (n)	1	2	1	
Dyspnea (n)	-	4	-	
Hospitalization (n, %)	-	4 (21%)	-	0.263
IgA ratio [median (min-max)]	1.67 (0.73-8.59)	1.53 (0.32-5.35)	1.17 (0.05-5.35)	0.491
IgG ratio				
Day 0 (mean ± SD)	4.68±3.21	2.72±2.40	4.34±1.82	0.814
Day 90 (mean ± SD)	3.42±2.26	2.92±2.24	2.09±1.07	0.204
Day 180 (mean ± SD)	2.42±1.05	1.94±1.54	1.43±0.95	0.088

b-DMARD: Biologic disease modifying anti-rheumatic drugs, CAPS: Cryopyrin-associated periodic syndromes, c-DMARD: Conventional disease modifying anti-rheumatic drugs, DADA2: Deficiency of adenosine deaminase-2, FMF: Familial Mediterranean Fever; Ig: Immunoglobulin, JIA: Juvenile idiopathic arthritis, SLE: Systemic lupus erythematosus, min-max: Minimum-maximum, SD: Standard deviation

Table 2. Comparison of IgG ratios of all participants measured at three different times

	df	MS	F	p-value
Comparison of IgG ratios on day 0 and day 180	1.267	37.567	10.065	**0.002**
Comparison of IgG ratios on day 0 and day 90	1	21.122	3.184	0.085
Comparison of IgG ratios on day 90 and day 180	1	26.582	23.460	**<0.001**

Ig: Immunoglobulin

biological treatment: 6, those with IRD not under biological treatment: 19) were monitored for six months in this study. At the end of the six-month for each subject, a significant decrease was found in the SARS-CoV-2 IgG levels. While no significant decrease was observed in the first trimester, there was a sharp decrease in the second trimester. Nonetheless, most subjects (77%) remained seropositive after six months. Age, gender, presence of IRD, and use of biological agents did not affect the decreasing pattern of the antibodies.

There are scarce data regarding the antibody screening acquired by SARS-CoV-2 infection in children with IRD. A study from the United Kingdom evaluated the IgG levels against the seasonal coronaviruses of children with SLE, JIA, juvenile dermatomyositis, and healthy children by using the blood samples of these donors who were collected before the COVID-19 pandemic. Children with IRD were found to present comparable or stronger humoral immune responses than healthy children, even if they were under immunosuppressive medication.[15] The seroprevalence of SARS-CoV-2 in pediatric rheumatic patients was screened in New York, and 35 of 262 subjects were found to be SARS-CoV-2 IgG positive. Out of 35 seropositive patients, 18 were under anti-tumor necrose factor, 2 were anti-interleukin (IL)-6, one was under anti-IL-1, and one was under Janus kinase inhibitor treatment. Thus, this study showed that children with IRD, including those receiving biological treatment, may produce proper antibodies following the infection.[16] However, there are several studies have evaluated the humoral responses after SARS-CoV-2 vaccinations of children with IRD. A study from Turkey demonstrated that pediatric rheumatic patients can mount a sufficient humoral response after two doses of the BNT162b2 mRNA vaccine.[17] Although antibody titers after the vaccines were significantly lower in the

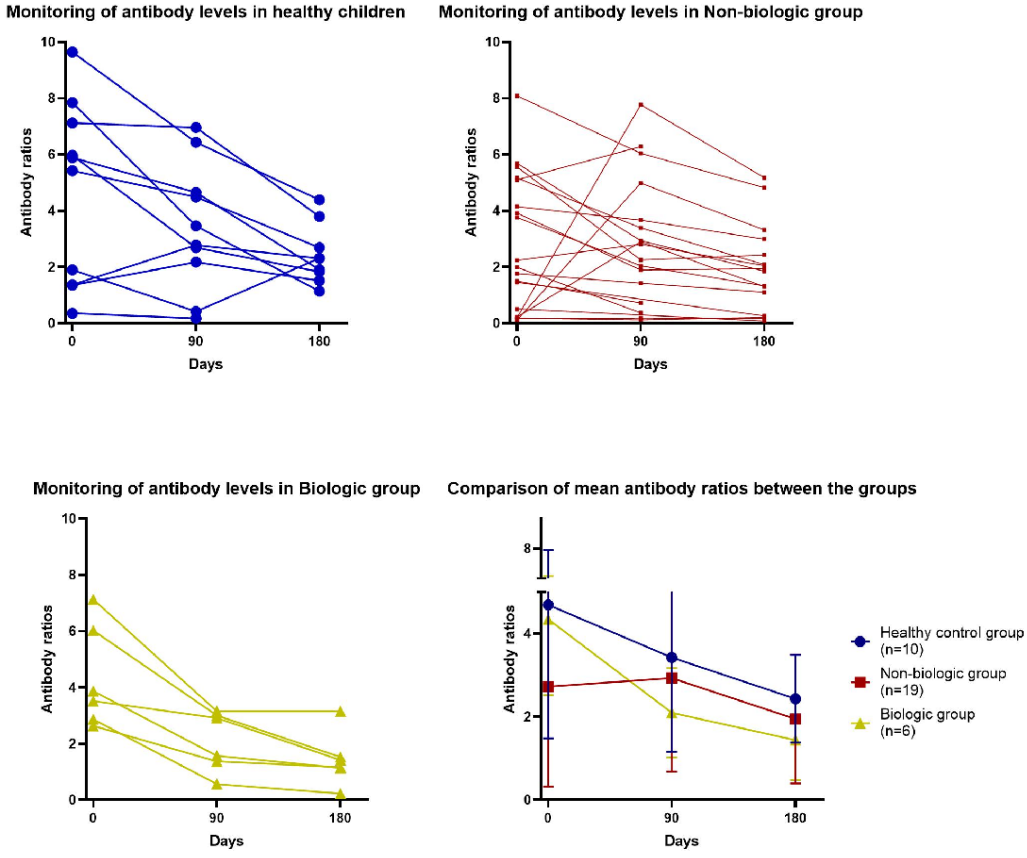

Figure 1. Anti-SARS-CoV-2 immunoglobulin G levels of the participants on day 0, day 90, and day 180

SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2

Table 3. The effects of variables on the change of immunoglobulin G ratios of all subjects at three different times

	Day 0 IgG ratio	Day 90 IgG ratio	Day 180 IgG ratio	df	MS	F	p-value
Gender				1.262	0.247	0.064	0.857
Male	2.88±2.19	2.13±1.45	1.77±0.97				
Female	3.95±2.89	3.37±2.87	2.08±1.47				
Rheumatic disease				1.258	4.505	1.207	0.292
Yes	3.11±2.34	2.71±2.01	1.80±1.40				
No	4.68±3.21	3.42±2.26	2.42±1.05				
Group				2.587	7.673	2.293	0.104
Biologic group	4.34±1.82	2.09±1.07	1.43±0.95				
Non-biologic group	2.72±2.40	2.92±2.24	1.94±1.54				
Healthy control group	4.68±3.21	3.42±2.26	2.42±1.05				
Contact history				1.269	0.908	0.237	0.687
Yes	4.29±2.60	3.38±2.21	2.50±1.40				
No	2.78±2.59	2.43±1.88	1.36±0.95				
Symptomatic infection				1.259	1.113	0.289	0.647
Yes	3.37±2.23	2.81±1.75	2.13±1.25				
No	3.67±2.94	2.98±2.29	1.89±1.40				
Ongoing treatment							
b-DAMRD	4.34±1.82	2.09±1.07	1.43±0.95	1.280	6.356	1.767	0.180
c-DMARD	3.86±2.49	2.52±1.71	2.01±1.32	1.265	1.066	0.278	0.656
Colchicine	3.00±2.60	2.61±1.80	1.91±1.41	1.262	1.214	0.316	0.630
Steroid	4.93±2.33	3.09±2.16	2.30±1.73	1.272	2.072	0.548	0.505
Hospitalization				1.274	5.006	1.366	0.259
Yes	3.21±2.77	4.25±3.08	2.78±2.08				
No	3.59±2.70	2.79±1.98	1.90±1.25				

b-DMARD: Biologic disease modifying anti-rheumatic drugs, c-DMARD: Conventional disease modifying anti-rheumatic drugs, Ig: Immunoglobulin

adolescents with IRD than in their healthy peers, the seropositivity rate was not significantly different between the groups in a study by Heshin-Bekenstein et al.[18] A study from Spain demonstrated that neither humoral nor the cellular response to the BNT162b2 mRNA vaccines was different between the adolescents with and without IRD.[19] In our study, neither IgA nor IgG levels were different between the healthy children and those with IRD at the baseline. Similarly, no significant difference was shown between adults with IRD and healthy adults regarding the antibody levels following SARS-CoV-2 infection in several studies.[20,21]

The most common disease of our subjects was JIA (n=9), which is also the most common rheumatic disease in the childhood,[22] and the others were FMF (n=8), SLE (n=5), Sjögren's disease (n=1), CAPS (n=1), and DADA2 (n=1), respectively. Healthy children were significantly younger, which may be related to a mix of a relatively increased propensity of the parents of the younger children with IRD to apply strict isolation measures and a general diagnostic delay of IRD in childhood.

While three patients with JIA were under adalimumab treatment, one with systemic subtype was receiving canakinumab. The other patient under canakinumab was a CAPS patient, and one patient with DADA2 was receiving etanercept during the study process. Although thirteen (37.1%) subjects had a history of symptomatic SARS-CoV-2 infection, only four of them (11.4%) required hospitalization, and all of them recovered completely. Eleven of the thirteen symptomatic patients and all hospitalized patients were rheumatic patients. Consistent with our data, both symptomatic infection and hospitalization were found to be significantly more common in children with IRD than in healthy children in a previous study.[12]

While the most common symptoms of COVID-19 in the pediatric age are cough, pharyngeal erythema, and fever,[23] the most common ones in our study were fatigue, cough, sore throat, and myalgia. Only four of our thirty-five subjects had a fever, and this relatively decreased frequency of fever may be attributed to the fact that most of our subjects were under anti-inflammatory treatment regimens during the study.

Twenty-seven participants (77.1%) remained seropositive at the end of the six-months during the observation period. Similarly, it was shown in a prospective study that monitored the antibody levels acquired by SARS-CoV-2 infection that 80% of seropositive adults with SLE remained in their initial serological status until 30 weeks later.[24]

At the end of the six-month duration period of our study, a significant decrease, which was mainly observed in the second trimester, was found in the IgG levels of the participants. None of the tested variables, such as age, gender, presence of IRD, and use of biological agents, affected this decrease. Consistent with our results, Boekel et al.[25] showed that age, gender, hospitalization history, and receiving cDMARD/bDMARD except B-Cell targeting agents do not affect the development of long-lasting humoral immunity after the SARS-CoV-2 infection. However, none of our subjects were under rituximab treatment, which resulted in complete B lymphocyte depletion.

Study Limitations

The main limitation of the study is the limited number of cases. Unfortunately, we did not perform a power analysis due to the following reasons: 1) There is no study so far similar to ours. 2) We conducted this study among the seropositive subjects. Therefore, even if we need more patients to establish the optimal sample size, it is impossible to find. 3) Rheumatic diseases are seen very rare in childhood, already. 4) The costs of antibody measuring commercial kits are a significant economic burden. 5) There is a general unwillingness of asymptomatic SARS-CoV-2 seropositive children's parents to regular follow-up for antibody monitoring. Other limitations were that we could not assess the effects of immunosuppressive dosages, the durations of the diseases, and the medication lengths of the patients on the decreasing pattern of the antibodies due to the unavailable data. Additionally, the heterogeneity of the rheumatic diseases of our patients is another limitation, which can interfere with antibody levels in different ways. However, the main strength of our paper is that this is the only study to our best knowledge that presents the SARS-CoV-2 antibody levels acquired by the natural infection of children with IRD at three different times.

CONCLUSION

Although they decrease rapidly in the second trimester, we showed that antibodies acquired by infection in healthy children and children with IRD mostly stay at an acceptable level after six months. These data can be used to schedule vaccination programs. Besides, we showed that IRD and biological drugs do not affect the decrease in antibody levels. Therefore, no additional precautions may be required regarding vaccination in this patient group. However, due to the limited number of patients, the data of our study should be confirmed with studies involving a larger number of patients.

Ethics

Ethics Committee Approval: The study protocol was approved by the Institutional Ethics Committee of İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine (approval number: 04/16/20–29430533-604.01-01-54959).

Informed Consent: Written informed consent was obtained from the participants included in this study and no identifying information of any participant was included in this paper.

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Authorship Contributions

Surgical and Medical Practices: F.H., S.Ş., O.K., A.A., V.G., G.Y., G.İ., Ö.K., K.B., Concept: M.Y., A.A.Y., B.S.K., Ö.K., K.B., Design: B.S.K., K.B., Data Collection or Processing: F.H., D.Ö., S.Ş., O.K., A.A., V.G., G.Y., G.İ., Ö.K., K.B., Analysis or Interpretation: F.H., D.Ö., K.B., Literature Search: F.H., D.Ö., M.Y., A.A.Y., B.S.K., Ö.K., K.B., Writing: F.H., K.B.

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Original Article

Serum Vitamin D and B12 Levels in School-aged Children and Adolescents with Frequent Primary Headache Attacks

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ABSTRACT

Objective: Headaches are among the most frequent disorders in children and adults. Recent evidence suggests that various neurological disorders, including headaches, epilepsy, and neurodegenerative disorders, are associated with deficiencies in vitamins D and B12. In this context, this study aims to compare serum vitamin D and B12 levels in pediatric patients with migraine or tension-type headaches with those of healthy children and to explore the relationship between the frequency of headache attacks and the deficiencies in the aforementioned vitamins.

Methods: The population of this retrospective study consisted of pediatric patients who presented with a headache lasting at least six months to the pediatric neurology outpatient clinics. The patients included in the study sample were categorized into two groups: Patients with migraines (n=54) and tension-type headaches (n=72). Additionally, 64 children without headaches were included in the control group. Detailed data on the features of headaches were obtained from the patients or their parents. Patients were categorized into three groups according to the frequency of the headaches as patients who had headache attacks a) once a week, b) twice or three times a week and c) ≥ four times a week. The patients were grouped into four grade levels based on their PedMIDAS scores. All participants included in the study were subjected to thyroid function tests, and vitamin D and vitamin B12 levels.

Results: There was no significant difference between the groups in serum vitamin B12 levels ($p>0.05$). However, the median vitamin D level was significantly higher in patients with migraine-type headaches ($p<0.001$). The rate of patients with vitamin D deficiency was significantly lower in the tension-type headache group than in the migraine group ($p=0.005$). There was no significant correlation between the Pediatric Migraine Disability Assessment (PedMIDAS) grades and vitamin B12 levels ($p>0.05$). However, the serum vitamin D levels of patients with a PedMIDAS grade between 1 and 3 were significantly higher in patients with migraine than in those with tension-type headaches ($p<0.05$). The serum vitamin D levels of migraine patients with a PedMIDAS grade of 4 were significantly lower than those of migraine patients with a PedMIDAS grade of 3 ($p=0.018$). The migraine patients with one and 2-3 attacks per week had significantly higher vitamin D levels than those patients with tension-type headaches ($p=0.031$ and $p<0.001$, respectively). Additionally, the vitamin D levels in migraine patients with ≥4 attacks per week were significantly lower than those of migraine patients with 2-3 attacks per week ($p=0.010$).

Conclusion: The patients with migraine and higher frequency of attacks had lower vitamin D levels.

Keywords: Vitamin D, children, migraine, tension-type headache, vitamin B12 deficiency

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INTRODUCTION

Headaches are the most common neurological symptom among children and adolescents who seek medical consultations.[1-3] Headaches are also the leading cause of school absenteeism. Headache prevalence increases throughout childhood and peaks at approximately 11-13 years, regardless of gender. A student-based epidemiological study in Türkiye reported that the prevalence of recurrent headache attacks in adolescents aged 12 to 17 was 52.2%[4]. Most cases present with a benign course secondary to primary headache disorders such as tension-type headaches and migraine, whereas in some cases, headaches might also be associated with severe intracranial pathologies.[2,5,6] It has been reported in the literature that tension-type headaches and migraine are the two most common headache diagnoses, in decreasing order, among Turkish adolescents.[5] However, the exact pathophysiology and predisposing factors remain controversial, particularly for primary headache disorders.[2,7]

The proper diagnosis of a primary headache disorder and its management significantly impact school life, daily life productivity, and overall quality of life in the pediatric population. Prophylactic therapy and lifestyle changes may help reduce the frequency and severity of headache attacks in children with chronic headaches. In addition to using medications such as antiepileptics or antidepressants, treatment modalities based on dietary ingredients, including vitamins, minerals, herbs, or other botanicals, are used for treating primary headaches.[8] Given its potential role in the pathogenesis of various neurological diseases, the possible role of vitamin D in headache prophylaxis has been mentioned in the literature.[9-12] Vitamin B12 is another essential vitamin that plays a key role in the central nervous system. However, the number of studies on the potential role of vitamin B12 levels among different pediatric headache groups is limited.[13,14] Although vitamin D and B12 deficiency/insufficiency have been reported frequently in patients with migraine in recent studies, there is no consensus on prescribing these vitamins in routine clinical practice.

In this context, this study was conducted to compare the serum vitamin D and B12 levels in pediatric patients with migraine and tension-type headaches with those of healthy children and to determine the relationship between the frequency of headache attacks and serum vitamin D and B12 levels.

MATERIALS AND METHODS

Research Design

The protocol of this retrospective study was approved by the Erciyes University Clinical Research Ethics Committee (decision no: 2016/479, date no: 12.08.2016). The study was conducted in accordance with the principles set forth in the Declaration of Helsinki. Patients' legally authorized representatives provided informed consent for patient information to be published.

Population and Sample

The population of this retrospective cohort study consisted of pediatric patients (aged between 6 to 18 years) who presented with a headache lasting at least six months to the Pediatric Neurology Outpatient Clinics. Patients' data were obtained from their medical records available in the hospital medical record/database. The diagnoses of primary headaches, i.e., migraine and tension-type headache, were made based on the 3rd edition of the criteria of the International Classification of Headache Disorders[15]. Accordingly, patients diagnosed with a primary headache were included, whereas patients on vitamin D and B12 medication, patients with headaches secondary to diseases such as brain tumors, paranasal sinus diseases, infections, other systemic diseases, and vision problems, as well as patients with any neurological disorders other than headaches were excluded from the study to avoid any confounding effects.

The control group consisted of children randomly selected using a random sequence number generator from the children with age and gender characteristics that match those of the patient group who were admitted to the general pediatric outpatient clinic in the same period for routine examination and did not have a history of headaches and have not been receiving any vitamin supplementation.

The same pediatric neurologist performed all the patients' physical and neurological examinations. Detailed data on the features of headaches, such as the frequency of headaches, were obtained from the patients or their parents. Patients were categorized into three groups according to the frequency of the headaches as patients who had headache attacks a) once a week, b) twice or three times a week, and c) ≥ four times a week.

All patients underwent an ophthalmological examination. In cases where deemed necessary, patients also undergo brain magnetic resonance imaging and/or electroencephalogram examinations.

Questionnaire

The headache-related functional impairment of the children in school and at home was evaluated using the 6-item Pediatric Migraine Disability Assessment (PedMIDAS) tool for three months.[16] The total PedMIDAS scores were calculated using the method described by Hershey et al.[17] The total number of days the children were affected by the headache attacks during the last three months was determined.[16,18] The patients were grouped into four grade levels based on their PedMIDAS scores: Grade 1: No or slight impairment (scores 0-10), grade 2: Mild impairment (scores 11-30), grade 3: Moderate impairment (scores 31-50), and grade 4: Severe impairment (scores >50).

Laboratory Tests

Blood samples were obtained from all subjects after overnight fasting. Patients' serum vitamin D and B12 levels were routinely measured in the pediatric outpatient clinic per the institutional policy. The collected blood samples were centrifuged at 4000 rpm

at room temperature. The serum vitamin D levels were evaluated by the two step competitive binding immunoenzymatic assay method. Vitamin D levels >30 ng/mL were considered normal, whereas vitamin D levels ≤30 ng/mL were considered deficient.[9]

The electrochemiluminescence immunoassay procedure was used to measure the serum vitamin B12 levels. Vitamin B12 levels <200 pg/mL were considered deficient, whereas vitamin B12 levels <160 pg/mL were considered severely deficient.[2]

Statistical Analysis

The descriptive statistics obtained from the collected research data were expressed as mean ± standard deviation values in the case of normally distributed continuous variables, as median and minimum - maximum values in the case of non-normally distributed continuous variables, and as numbers and percentage values in the case of categorical variables. The Shapiro-Wilk, Kolmogorov-Smirnov, and Anderson-Darling tests were used to analyze the normal distribution characteristics of the numerical variables.

The independent samples t-test and the Mann-Whitney U test were used to compare two independent groups in the case of normally and non-normally distributed numerical variables, respectively. Pearson's chi-squared and Fisher's exact tests were used to compare the differences between categorical variables in 2x2 tables, whereas the Fisher-Freeman-Halton test was used to compare the differences between categorical variables in the RxC tables.

The one-way analysis of variance (ANOVA) test and the Kruskal-Wallis test were used to compare more than two independent groups in the case of normally and non-normally distributed numerical variables, respectively. In analyses featuring parametric tests, the differences between the groups were evaluated with the Games-Howell test, provided that the data were heterogeneous according to their distribution. However, in analyses featuring non-parametric tests, the Dwass-Steel-Critchlow-Fligner test was used to evaluate the differences between the groups.

The Jamovi project 2.2.5.0 (Jamovi, version 2.2.5.0, 2022, retrieved from https://www.jamovi.org) and JASP 0.16.1 (Jeffreys' Amazing Statistics Program, version 0.16.1, 2022, retrieved from https://jasp-stats.org) software packages were used in the statistical analyses. Probability (p) statistics ≤0.05 were deemed to indicate statistical significance

RESULTS

The distribution of patients' demographic and clinical characteristics by the group is shown in Table 1. There were 72 patients (47 girls/25 boys) with tension-type headaches, 54 patients with migraine (37 girls/17 boys), and 64 healthy children (20 girls/34 boys). There was no statistically significant difference between the groups in age and gender (p>0.05).

The distribution of the frequency of attacks and PedMIDAS grades by the study groups is given in Table 2. Accordingly, there was no significant difference between the patients with tension-type headaches and migraine in the frequency of attacks and PedMIDAS grades (p=0.388 and p=0.551, respectively).

There was no significant difference between the groups in terms of serum B12 levels (p>0.05) (Table 3). The incidence of vitamin B12 deficiency was 19.4% among patients with tension-type headaches, 13.0% among patients with migraine, and 14.1% among healthy children. There were more patients with vitamin B12 deficiency in the tension-type headache group than in the migraine group and the healthy control group; however, the difference between the groups was insignificant (p=0.551). However, the groups significantly differed in serum vitamin D levels and the rate of patients with vitamin D deficiency (p<0.001 and p=0.005, respectively) (Table 3). Accordingly, the median vitamin D levels were significantly higher among patients with migraine (p<0.001). In parallel, the rate of patients with vitamin D deficiency was significantly higher among patients with tension-type headaches (p=0.005). Paired comparison of the patients with tension type-headache and migraine revealed similar results (Table 4).

There was no significant difference in the serum vitamin B12 levels between patients with different PedMIDAS grades for each group (p>0.05) (Table 5).

The serum vitamin D levels of patients with PedMIDAS grades 1 to 3 were significantly higher in patients with migraine than in those with tension-type headaches (p<0.05) (Table 5). The serum vitamin D levels of migraine patients with a PedMIDAS grade of

Table 1. Demographic and clinical characteristics of the study groups

	Patients with tension-type headache (n=72)	Patients with migraine (n=54)	Control (n=64)	p-value
Age (year)[§]	13.5 (6.0-18.0)	13.5 (8.0-18.0)	13.8 (7.8-17.6)	0.969**
Sex[‡]				
Male	36 (50.0)	22 (40.7)	34 (53.1)	0.384*
Female	36 (50.0)	32 (59.3)	30 (46.9)	

[‡]n (%), [§]median (minimum-maximum)
*Pearson chi-square test, **Kruskal-Wallis H test

Table 2. Clinical characteristics of the patients with tension-type headache and migraine

	Patients with tension-type headache (n=72)	Patients with migraine (n=54)	p-value
Frequency of attacks‡			
1 per week	24 (33.3)	24 (44.4)	0.388*
2-3 per week	27 (37.5)	19 (35.2)	
≥4 per week	21 (29.2)	11 (20.4)	
PedMIDAS grades‡			
Grade 1	24 (33.3)	24 (44.4)	0.551*
Grade 2	14 (19.4)	11 (20.4)	
Grade 3	13 (18.1)	8 (14.8)	
Grade 4	21 (29.2)	11 (20.4)	

‡n (%), §Median (minimum-maximum)
*Pearson chi-square test.
**Kruskal-Wallis H test.
PedMIDAS: Pediatric Migraine Disability Assessment

4 were significantly lower than those of migraine patients with a PedMIDAS grade of 3 (p=0.018).

There was no significant difference between migraine patients with other PedMIDAS grades in terms of vitamin D levels (p=0.663).

There was no significant correlation between vitamin B12 levels and the frequency of attacks between the study groups (p>0.05) (Table 6). However, the migraine patients with one and 2-3 attacks per week had significantly higher vitamin D levels than those patients with tension-type headaches (p=0.031 and p<0.001, respectively). Additionally, the vitamin D levels in migraine patients with ≥4 attacks per week were significantly lower than those of migraine patients with 2-3 attacks per week (p=0.010).

DISCUSSION

Vitamin B12 and D play critical regulatory functions in brain development, cell differentiation, and apoptosis. In this context, this study explored the relationship, if any, between B12 and D vitamin levels and the frequency of migraine and tension-type headaches in the pediatric population. Although clinical neurological manifestations of low levels of vitamins in children

Table 3. Comparison of the laboratory parameters among study groups

	Patients with tension-type headache (n=72)	Patients with migraine (n=54)	Control (n=64)	p-value
Vitamin B12 (pg/mL)§	271.0 (92.0-679.0)	324.9 (94.0-682.5)	299.5 (63.0-714.0)	0.202*
≥200 pg/mL‡	58 (80.6)	47 (87.0)	55 (85.9)	0.551**
<200 pg/mL‡	14 (19.4)	7 (13.0)	9 (14.1)	
Vitamin D (pg/mL)§	13.0 (3.5-50.0)	20.8 (5.0-53.0)	15.9 (7.7-41.1)	**<0.001*** **
≥30 pg/mL‡	2 (2.8)[a]	11 (20.8)[b]	7 (10.9)[a,b]	**0.005****
<30 pg/mL‡	70 (97.2)[a]	42 (79.2)[b]	57 (89.1)[a,b]	

‡n (%), §Median (minimum-maximum)
[a,b]Different letters in the same row shows a significant difference.
*Mann-Whitney U test, **Pearson chi-square test, Fisher's exact test, or Fisher Freeman Halton test, ***Kruskal Wallis-H test.
Pairwise comparisons with Dwass-Steel-Critchlow-Fligner test.

Table 4. Comparison of the laboratory parameters between patients with tension-type headache and with migraine

	Patients with tension-type headache (n=72)	Patients with migraine (n=54)	p-value
Vitamin B12 (pg/mL)§	271.0 (92.0-679.0)	324.9 (94.0-682.5)	0.085*
≥200 pg/mL‡	58 (80.6)	47 (87.0)	0.469**
<200 pg/mL‡	14 (19.4)	7 (13.0)	
Vitamin D (pg/mL)§	13.0 (3.5-50.0)	20.8 (5.0-53.0)	<0.001*
≥30 pg/mL‡	2 (2.8)	11 (20.8)	0.003**
<30 pg/mL‡	70 (97.2)	42 (79.2)	

‡n (%), §Median (minimum-maximum)
*Mann-Whitney U test, **Pearson chi-square or Fisher's exact test

with primary headaches have been described in several case studies, the underlying mechanism of the frequency of headache attacks is not yet fully understood.[19] The results of this study, contrary to Ayanoğlu et al.[6], did not reveal any significant difference between the study groups in serum vitamin B12 levels. However, there was a significant difference between the groups in serum vitamin D levels. Accordingly, there was a significant correlation between low levels vitamin D in pediatric patients with migraine and a higher frequency of attacks. Additionally, there were significant relationships between the vitamin D levels, the PedMIDAS grades, and headache frequency.

Migraine is considered a complex neurological disorder involving interacting environmental and hereditary factors. Migraine prophylaxis supplements are used to prevent and/or alleviate headache attacks by improving mitochondrial function and energy production in neurological systems. This mechanism might be responsible for the pathogenesis of migraine[20]. The literature on vitamin D levels and headaches in children is sparse and contradictory. In one of these studies exploring the potential risk factors for primary headaches in children, Al Momani et al.[3] found that abnormal vitamin D levels were significantly associated with primary headaches. Similarly, the tension-type headache and migraine groups included in this study significantly differed in vitamin D levels. Yang et al.[21] reported a potential correlation between vitamin D deficiency and headaches. However, Kjaergaard et al.[22] reported a possible link between vitamin D levels and tension-type headaches but could not propose a correlation between vitamin D levels and migraine. There are several definitions of vitamin D deficiency. Vitamin D deficiency is most commonly characterized by plasma vitamin D levels of <10 ng/mL. However, the threshold level for vitamin D insufficiency is still a matter of debate[23]. The discrepancies in the literature on vitamin D levels and headaches in children may, in part, be attributed to the use of said different criteria for defining vitamin D deficiency. Furthermore, the migraine patients with higher PedMIDAS grades (grade 4) and frequent headache attacks (≥4 per week) in this study had significantly lower vitamin D levels. In line with the findings of this study, Kılıç and Kılıç[24] reported a negative correlation between the frequency of migraine attacks and serum vitamin D levels and determined that patients with pain are commonly advised to take vitamin D supplements, considering that vitamin D may reduce the frequency of migraine attacks. Similarly, Gungör et al.[9] reported that as the vitamin D levels decreased, the severity of the headache significantly increased, resulting in higher MIDAS grades.

Vitamin D reportedly exhibits an anti-inflammatory effect through the prevention of neuroinflammation that produces migraine and tension-type headaches.[11,25] Vitamin D balances T helper and regulatory T-cells to inhibit prostaglandin E_2 synthesis by reducing nitric oxide production.[26] Additionally, vitamin D is responsible for the upregulation of growth factor beta-1 and interleukin-4 and suppresses tumor necrosis factor-α[27]. The anti-inflammatory effect of vitamin D has also been explained by the inverse relationship between the C-reactive protein and vitamin D levels.[28] Hence,

Table 5. Comparison of vitamin B12 and D levels based on the PedMIDAS grades

	Patients with tension-type headache (n=72)	Patients with migraine (n=54)	p-value
Vitamin B12 (pg/mL)†			
PedMIDAS grades			
Grade 1	304.0±123.9	314.7±97.6	0.741*
Grade 2	300.1±128.1	376.4±166.6	0.225*
Grade 3	286.4±141.5	325.4±106.9	0.483*
Grade 4	304.1±122.7	289.6±130.1	0.763*
p**	0.979	0.395	
Vitamin D (pg/mL)§			
PedMIDAS grades			
Grade 1	16.5 (4.0-28.0)	20.8 (5.0-53.0)	**0.031*****
Grade 2	11.0 (6.0-25.0)	25.3 (10.0-43.0)	**0.007*****
Grade 3	12.0 (7.0-34.0)	27.3 (18.0-53.0)	**0.003*****
Grade 4	13.0 (3.5-50.0)	11.0 (7.0-49.5)	0.606***
p****	0.663	**0.018**	

†Mean ± standard deviation, §Median (minimum-maximum)
*Independent Samples t-test, **One-way ANOVA test, ***Mann-Whitney U test, ****Kruskal-Wallis H test.
Pairwise comparisons with Dwass-Steel-Critchlow-Fligner test.
PedMIDAS: Pediatric Migraine Disability Assessment

Table 6. Comparison of vitamin B12 and D levels based on the frequency of headache attacks

	Patients with tension-type headache (n=72)	Patients with migraine (n=54)	p-value
Vitamin B12 (pg/mL)†			
Frequency of attack			
1 per week	314.5 (95-624)	339 (94-475)	0.529*
2-3 per week	265 (92-590)	320 (165-682.5)	0.069*
≥4 per week	258 (171-679)	320 (100-519)	0.736*
p**	0.744	0.852	
Vitamin D (pg/mL)§			
Frequency of attack			
1 per week	16.5 (4-28)	20.8 (5-53)	**0.031***
2-3 per week	12 (6-34)	26.6 (10-53)	**<0.001***
≥4 per week	13 (3.5-50)	11 (7-49.5)	0.606*
p**	0.497	**0.010**	

†Mean ± standard deviation. §Median (minimum-maximum)
*Mann-Whitney U test, **Kruskal-Wallis H test.
Pairwise comparisons with Dwass-Steel-Critchlow-Fligner test

the increase in the frequency of headache attacks in pediatric migraineurs included in this study is explained by the low serum vitamin D levels.

Patients with pain are advised to take vitamin D supplements since vitamin D may reduce the number of headache attacks in some patients, particularly patients with migraine. This positive effect of vitamin D is even more pronounced if the patients are vitamin D deficient. As a matter of fact, in a study conducted with 53 pediatric migraine patients, Cayir et al.[29] reported that vitamin D therapy and anti-migraine prophylactic treatment reduced the number of migraine attacks. In comparison, this study examined the effect of vitamin D levels on the number of childhood primary headache attacks. Studies on the effects of vitamin D deficiency and/or insufficiency among pediatric patients with tension-type headaches are limited. In a case series by Prakash and Shah[30] conducted with eight adult patients with chronic tension-type headaches and vitamin D deficiency, vitamin D and calcium supplementation was found to be beneficial in all patients, and thus, they speculated on the possible mechanisms for headaches in relation to vitamin D deficiency. Nevertheless, the effect of vitamin D and B12 supplements on the course of tension-type headaches in the pediatric population is needs to be determined. To the best of this study's authors' knowledge, this is the first study that assessed the relationship between vitamin D levels and the number of attacks comparatively between migraine and tension-type headaches in the pediatric population.

The lack of detailed clinical data, i.e., the severity of the headache and medication used, might be considered a limitation of this study.

CONCLUSION

The study findings revealed a significant relationship between migraine attacks and vitamin D levels in pediatric patients. Therefore, vitamin D supplementation may help prevent headache attacks in this patient population, particularly in migraine patients with a higher frequency of headaches. Additionally, no significant correlation was found between vitamin B12 levels and the total number of days the tension-type headache patients were affected by the headache attacks. The findings of this study support and contribute to the explanation of different mechanisms between migraine and tension-type headaches, the most common headache types seen in children. Randomized clinical trials with larger samples will be required to corroborate the findings of this study.

Ethics

Ethics Committee Approval: The protocol of this retrospective study was approved by the Erciyes University Clinical Research Ethics Committee (decision no: 2016/479, date no: 12.08.2016).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: G.D.K.Ö., M.C., S.K., Design: G.D.K.Ö., E.S., Data Collection or Processing: G.D.K.Ö., M.C., F.K., M.K., H.G., H.P., S.K., Analysis or Interpretation: G.D.K.Ö., Literature Search: G.D.K.Ö., Writing: G.D.K.Ö., E.S.

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Original Article

Evaluation of Complications Associated with Cardiac Catheterization: A Single-center Experience

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ABSTRACT

Objective: The aim of this study is to evaluate complications of cardiac catheterization (CC) procedures in a pediatric cardiology center.

Methods: The clinical records of 781 cardiac catheterizations were reviewed to identify procedure-associated complications. Catheterizations were grouped as diagnostic or interventional procedures. A complication was classified as a major or a minor.

Results: Patient ages ranged from 1 day to 28.8 years (median 3.3 years). Interventional catheterizations represented 58.5% of total procedures. Patent ductus arteriosus (PDA), atrial septal defect (ASD), and aortic coarctation were the most common diagnoses in our cohort. PDA occlusion, ASD closure, pulmonary valvuloplasty, angioplasty/stenting for aortic coarctation, and aortic valve dilation were the most commonly performed interventional catheterizations. Complications were detected in 17.5% of all procedures. Major complications were 2.3% for all procedures. Decreased/absent pulses were the most common complication in all categories (8.1%). The mortality rate of cardiac catheterization procedures was 0.5%. Relative to diagnostic procedures, interventional catheterizations were associated with a greater risk of complications.

Conclusion: Our study's success and complication rates were similar to other studies. Complications of CC depend on the severity of the underlying congenital heart disease and the type of procedure.

Keywords: Cardiac catheterization, complication, patent ductus arteriosus, atrial septal defect, aortic coarctation

INTRODUCTION

Congenital heart disease (CHD) is observed in approximately 0.8% of all live births. In the first year of life, 2-3 of 1000 newborns may be symptomatic due to CHD. CHD is usually diagnosed within the first week in 40-50% and within the first month in 50-60%. Due to advances in surgery, the number of children with CHD reaching adulthood has increased.[1]

Cardiac catheterization (CC) is used in cardiac diseases to determine the anatomy before surgery, evaluate the presence and size of the shunt, calculate pulmonary vascular resistance, evaluate the response to vasodilator agents and oxygen, monitor CHD after surgery, take a myocardial biopsy, electrophysiological studies, and in transcatheter ablation. Although it is highly invasive and may have serious complications, CC and angiocardiography, which have been used for many years in the definition of cardiac anatomy and physiology, have also been widely used in therapeutic interventions with the development of technology and have been an alternative to surgical treatment in some cases.[1,2]

Complications of the commonly used CC procedures are important in terms of morbidity and mortality. The overall mortality rate has

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been reported as 0.1%. This rate is higher (1-2%) in newborns with critical CHD.[2] Morbidities such as dysrhythmia, cardiac perforation and neurological issues due to hypoxia are rare, on the other hand, minor complications such as mild bleeding, weak pulses are common and frequency varies according to the clinical condition of the patient and the experience of the clinic. Determining the complication types and frequencies and reviewing their causes will be useful in preventing complications that may develop in subsequent procedures.

Our study aimed to evaluate the complications of diagnostic and therapeutic CC procedures performed at İstanbul University, İstanbul Faculty of Medicine, Department of Pediatric Cardiology.

MATERIALS AND METHODS

Study Design and Patients

The patients who underwent CC between January 2007-June 2011 at İstanbul University, İstanbul Faculty of Medicine, Department of Pediatric Cardiology, constituted the study group. Demographic data and details of the catheterization procedures were obtained from the computer database, patient files, and catheterization records, retrospectively. According to the data obtained from these records, 781 catheterization procedures were performed in 708 patients.

According to body weight, groups were classified as <5 kg, 5.0-9.9, 10.0-19.9, 20.0-39.9, and more than 40 kg. Standard deviation values were calculated according to body weight reference values in children older than 6 months.[3,4] Cardiac diseases were grouped as cyanotic or acyanotic.[1] The catheterization procedure groups were grouped as diagnostic or interventional. The therapeutic procedures were defined as interventional, whereas the others were defined as diagnostic. Complications were defined as major or minor.

Complications were defined as below:

Absent/decreased pulses: The condition of absent or low pulses distal to the catheter entry site after the procedure requires treatment. Pulse weakness that did not require treatment and regressed spontaneously was not considered a complication. Those requiring anticoagulant and/or thrombolytic therapy were classified as minor, and those requiring surgical thrombectomy were classified as major complications.

Bleeding: Bleeding that occurred from the catheter entry site and required transfusion during or after catheterization. Bleeding that did not require transfusion was not considered a complication. In the case of shock, the complication was classified as major. Patients with the coexistence of absent/decreased pulses and bleeding were considered as having local vascular complications.

Device embolization: Complications were considered minor if the embolized device was removed by catheterization, and major if the device was surgically removed.

Neurological complications: Cerebrovascular accident (CVA), convulsion, change in consciousness without the hemodynamic disorder, sensory deficit, and acute vision problems were defined as neurological problems (major in case of permanent impairment and minor in transient disorders).

Hypertension: A hypertensive attack that develops after catheterization was considered a complication. Hypertensive attacks requiring respiratory and circulatory support were grouped as major and others as minor.

Infection: Fever requiring antibiotic treatment after the CC was considered a complication. Persistent fever, sepsis, and/or infective endocarditis were considered major, while the others were classified as minor.

Allergic reaction: Urticaria, anaphylaxis and other allergic reactions were considered a complication. Anaphylaxis requiring respiratory and circulatory support was grouped as major and other allergic reactions were grouped as minor.

Methemoglobinemia: Methemoglobin value more than 10% in the blood gas analysis was defined as methemoglobinemia. Those requiring respiratory and circulatory support were grouped as major and others as minor.

Dysrhythmia: Dysrhythmias that regressed during the procedure were classified as minor, and those requiring long-term treatment were classified as major.

Vascular injury: A venous and/or arterial injury requiring surgical treatment was considered a complication. Those requiring surgery had major complications.

Heart failure: Defined as the need for inotropic agents due to the procedure. Inotrope requirement was considered a major complication.

Respiratory arrest: Respiratory arrest during and during the first 24 h after the catheterization procedure, which did not result in death was considered a major complication.

Death: Death due to any cause in the first 24 h after the CC procedure was considered a major complication.

Statistical Analysis

Statistical analyses were performed using the SPSS software version 15 (LEAD Technologies Inc, 2006). Data were presented with n (%) for categorical data and mean ± standard deviation for numerical data. Chi-square tests were used for comparison of categorical data (Fisher's exact test was used when chi-square test assumptions do not hold due to low expected cell counts). In the comparison of independent 2 groups, student t-test was used if the data were normally distributed, and Mann-Whitney U test was used if the data were non-normally distributed. Type I error was determined as 5% and a p-value was <0.05 was considered statistically significant.

RESULTS

A total of 781 CC procedures were performed at the Department of Pediatric Cardiology in 708 patients (361 male/347 female) (twice in 47 patients and three times in 13 patients).

According to the procedural group, 58.5% (n=457) of the CCs were interventional, and 41.5% (n=324) were diagnostic. The ratio of interventional CCs was 87.1 and 56.1% in newborns and patients older than 28 days, respectively (p<0.001).

The median age of the patients at the time of the procedure was 3.3 years (range: 1 day-28.8 years; mean 5.0±5.0 years). The ratio of newborns was 7.9%, and the ratio of patients younger than 6 months was 21.4%. Nine patients underwent catheterization on the first postnatal day (eight interventional and one diagnostic due to hypoplastic left heart syndrome).

The most common diagnoses in patients who underwent CCs were PDA (13.8%), secundum ASD (11.4%), and aortic coarctation (11.1%). In 0.9% (n=7) of CCs, no pathological findings were detected. The study group was classified as acyanotic (n=522, 66.8%) and cyanotic CHD (n=252, 32.3%).

In 17 patients, 20 CCs were performed for evaluating coronary vessels. Seven diagnostic coronary catheterizations were performed in four patients with familial hypercholesterolemia (normal in one, and varying degrees of coronary stenosis in the others). Congenital coronary anomalies were detected in eight patients on diagnostic catheterizations. A giant aneurysm in the left anterior descending coronary artery and total obstruction in the right coronary artery were observed in a patient with Kawasaki disease. Interventional catheterization (coil closure of the fistula between the right coronary artery and the right ventricle) was performed in three of these 17 patients.

Interventional procedures constituted 58.5% (n=457) of the CCs. The most common interventional catheterizations were PDA closure (n=99, 21.7%); ASD closure (n=86, 18.7%); pulmonary balloon valvuloplasty (n=83, 18.0%); angioplasty/stenting of aortic coarctation (n=75, 16.4%) and aortic balloon valvuloplasty (n=46, 10.0%). In four catheterizations multiple procedures were performed simultaneously. The success rate in all interventional catheterizations was 91.5% (n=418). When the frequent interventional catheterizations were compared, no significant difference was found between the success rates (p=0.503). Success rates in PDA closure with a duct occluder (n=43) and a coil (n=56) were 97.7% and 98.2%, respectively. There was no significant difference between the methods in terms of success rate (p=0.850).

Pulmonary valvuloplasty was successful in 92.8% (n=77) n of the 83 patients. Although the mean age of patients (4.0±5.3 years, n=77) who had a successful procedure was higher than the mean age of unsuccessful cases (0.6±0.9 years, n=6), this difference was not statistically significant (p=0.070).

Evaluation of Complications

Complications occurred in 17.5% (n=137) of 781 CCs. The major complication rate was 2.3% (n=18). The overall mortality rate of CCs was 0.5% (n=4). The most common complication was the weakness of peripheral pulses [observed in 63 (8.1%)]. The distribution of complications is demonstrated in Table 1.

When complications were evaluated according to the type of procedure, the complication rate was significantly higher for interventional procedures (p<0.001). The complication rates according to the type of CCs are demonstrated in Table 2.

Table 1. Distribution of complications

	Minor n (%)	Major n (%)	Total n (%)
Absent/weak pulses	54 (6.9)	0 (0.0)	54 (6.9)
Bleeding (+ transfusion)	11 (1.4)	0 (0.0)	11 (1.4)
Bleeding (+ weak pulses)	9 (1.2)	0 (0.0)	9 (1.2)
Device embolization	8 (1.0)	3 (0.4)	11 (1.4)
Neurological complications	7 (0.9)	2 (0.3)	9 (1.2)
Dysrhytmia	6 (0.8)	1 (0.1)	7 (0.9)
Infections	6 (0.8)	0 (0.0)	6 (0.8)
Respiratory arrest	-	5 (0.6)	5 (0.6)
Hypertension	4 (0.5)	0 (0.0)	4 (0.5)
Allergic reactions	3 (0.4)	0 (0.0)	3 (0.4)
Methemoglobinemia	3 (0.4)	0 (0.0)	3 (0.4)
Hearth failure	-	2 (0.3)	2 (0.3)
Vascular damage	0 (0.0)	1 (0.1)	1 (0.1)
Other (hematuria, chest pain, cyanosis, bronchospasm)	8 (1.0)	0 (0.0)	8 (1.0)
Death	-	4 (0.5)	4 (0.5)
Total complications	**119 (15.2)**	**18 (2.3)**	**137 (17.5)**
No complication			**644 (82.5)**
Total cardiac catheterizations			**781 (100.0)**

Table 2. The complication rates according to the type of the cardiac catheterization procedure

	Diagnostic n (%)	Interventional n (%)	p-value
Complication			
(+)	34 (10.5)	103 (22.5)	<0.001
(-)	290 (89.5)	354 (77.5)	
Complication type			
Minor	30 (88.2)	89 (86.4)	0.783
Major	4 (11.8)	14 (13.5)	

In PDA closure (n=99), the complication rate was 15.2%. Complication rates were 11.6% and 17.9%, respectively, in patients who underwent "duct occluder" (n=43) and "coil" (n=56) procedures (p=0.392). The major complication rate for PDA closure was 1.0%. While no major complications were observed in PDA closure with a "coil," major complications were observed in only one procedure with a "duct occluder" (p=0.143). The most common complication in PDA closure was device embolization (n=6, 6.1%). A major complication was observed in only one of the device embolizations.

In ASD closure (n=86), the complication rate was 9.3% (n=8). Major complications were observed in three (3.5%) patients. The most common complication was neurological complication (n=4, 4.7%) with only one considered major. Device embolization occurred in two patients during ASD closure, and both underwent surgery.

In pulmonary valvuloplasty (n=83), complications developed in 20.5% (n=17) of the patients. The major complication rate was 3.6%. Methemoglobinemia developed in two and post-procedure infections in four cases. The mean age of patients who developed complications during pulmonary valvuloplasty was significantly younger. The mean age of the patients with major complications was significantly lower than the patients with minor complications (p<0.001).

In angioplasty/stenting of aortic coarctation (n=75), complications were observed in 34.7% (n=26) of the patients, with a major complication rate of 1.3% (n=1). Neurological complications developed in this case.

In aortic valvuloplasty (n=46), the complication rate was 32.6% (n=15). A major complication was observed in one case (2.2%), who died on the 3rd postnatal day. The most common complication was absent/weak pulses (n=10) and all were minor.

In VSD closure, there was no difference in the complication rate between the muscular and perimembranous types (p=0.836). The major complication rate in the VSD closure was 16.7%. While no major complications were observed in the perimembranous type, major complications were observed in two patients with the muscular type. Also, this difference also was not statistically significant. An inferior vena cava injury occurred in one patient, and a surgical correction was performed. Device embolization occurred in three of the patients, and since none of them required surgery, these were considered minor complications.

Complications were observed in 4/10 patients who underwent pulmonary valve perforation. A major complication was detected in only one case (respiratory arrest).

The number of patients according to the interventional procedure and complication type is demonstrated in Table 3.

Overall, absent/weak pulses were the most common complication (n=63, 8.1%). Nine of the patients with absent/weak pulses had bleeding at the catheter insertion site, requiring transfusion. The second most common complication type after local vascular complications was device embolization (n=11, 1.4%). Six of the device embolizations occurred in PDA closure, three in VSD closure, and two in ASD closure. Neurological complications were observed in nine (1.2%) cases. CVA developed in three patients (one bleeding and two infarcts). In cases with CVA, hemiplegia and central facial paresis developed, and convulsions were observed in one case. Three patients who underwent ASD closure had short-term blurred vision with normal imaging. In four cases, one with CVA, convulsions were observed after the procedure. Death occurred in four cases (0.5%) in the first 24 h after the procedure. The neonatal mortality rate is 3.2%, this rate is 0.3% for the post-neonatal period.

DISCUSSION

Cardiac catheterization procedures were first practiced in the 1950s, and it has also been used for therapeutic purposes since the 1970s.[5] Pediatric CC started in the 1970s in our center and has been used for interventional purposes since 1986. Our study aimed to evaluate the characteristics and complications of CC procedures.

In the haemodynamic and anatomical evaluation of complex heart diseases, CC plays a fundamental role. However, due to advances in non-invasive imaging methods, the rate of CC for interventional purposes has also increased. In this study, more than half of the catheterization procedures were interventional. This ratio was quite similar to the rate reported by Mehta et al.[6] (58%). Cassidy et al.[7] reported the rate of interventional CCs as 14% (n=1037). In the study by Vitiello et al.[8], the rate of interventional catheterization was 14% in 1987 and increased to 43% in 1993. Bergersen et al.[9] reported the rate of interventional catheterization as 67.4%. Considering the results of these studies, it was concluded that the rates of interventional use of CC have increased over the years.

Table 3. The complication rates according to the interventional procure and complication type

	Complication (+), n (%)*		Complication (-),* n (%)
	Minor, n	Major, n	
PDA closure	**15 (15.2)**		**84 (84.8)**
	14	1	
ASD closure	**8 (9.3)**		**78 (90.7)**
	5	3	
Pulmonary valvuloplasty	**17 (20.5)**		**66 (79.5)**
	14	3	
Angioplasty/stenting of aortic coarctation	**26 (34.7)**		**49 (65.3)**
	25	1	
Aortic valvuloplasty	**15 (32.6)**		**31 (67.4)**
	14	1	

*p>0.05

PDA: Patent ductus arteriosus, ASD: Atrial septal defect

Patients diagnosed with CHD in the antenatal/early postnatal period using non-invasive methods can be treated early with interventional CC. In our study, patients underwent catheterization on the first postnatal day, and almost all of these were interventional procedures. Additionally, the proportion of interventional catheterization was significantly higher in newborns. Mehta et al.[6] reported these ratios as 6% and 18%, respectively.

The ratio of normal results in catheterization procedures was less than 1% in our study population, indicating the success of non-invasive imaging methods.

We detected that the most frequently applied interventional procedures were; PDA closure, ASD closure, pulmonary balloon valvuloplasty, angioplasty/stenting of aortic coarctation, and aortic balloon valvuloplasty. In similar studies, the most frequently performed interventional procedure was PDA closure.[6,8] Our success rate of PDA closure was 98%, regardless of the device type. Jang et al.[10] reported a success rate of 97.4% in the PDA closure with different devices in 117 patients. In a 2007 study by Wang et al.[11] that included patients from different age groups (n=68), the success rate of PDA closure with "Amplatzer Duct Occluder" was 97.1%. In another study by the same group, in 45 infants, the success rate of PDA closure was 97.8%.[12]

Complications were observed in 17.5% of the CCs in this study. The minor and the major complication ratios were 15.2% and 2.3%, respectively. Compared to other studies, complication rates were higher according to Mehta et al.[6] (complication rate 7.8%), but similar to those of Huang et al.[13] (complication rate 18.6%). In the series of Tavli et al.[14], (n=230), the complication rate was reported as 14.3%. In a multicenter study by Bergersen et al.[9], (3185 catheterizations when biopsy cases were excluded), the complication rate was 17.2%.

Although some differences were seen for all complications in different studies, our major complication ratio was similar to other studies. Vitiello et al.[8] reported this ratio as 2.0%, Mehta et al.[6] reported 2.2%, Cassidy et al.[7] reported 2.3%, and Soylu[15] reported 2.7%.

We have reported that the mortality 24 h after CC is 0.5%. Vitiello et al.[8] reported a mortality ratio of 0.14%, Mehta et al.[6] 0.23%, and Bergersen et al.[9] reported as 0.35%. The cause of death may not be determined in patients who undergo CCs, since there are also serious cardiac pathologies that may cause death. It may not be appropriate to consider these deaths only as complications of catheterization. Depending on the severity of the cases, different mortality rates may occur between series. While our study's neonatal mortality ratio was 3.2%, Mehta et al.[6] reported this as 7.1%.

The complication ratio in interventional procedures was significantly higher than in diagnostic procedures in our cohort. Bergersen et al.[9] similarly reported high complication ratios in interventional procedures. The high ratio of interventional procedures also increases the overall complication ratio. In the study by Vitiello et al.[8], the ratio of interventional procedures was 28%, and the complication ratio in interventional procedures was 13.2%, while the overall complication ratio was 8.8%.

The ratio of major complications was also higher for interventional procedures compared to diagnostic procedures in our study. In the study of Bergersen et al.[9], major complication ratios were also higher in interventional than in diagnostic procedures.

Neurological complications were most common in ASD closure and device embolization occurred in two cases. In the study of Lin et al.[16], device embolization was observed in one of 33 cases and a complete AV block was observed in one case. Two device embolizations were reported by Wilson et al.[17] in a case series of 227 children and adults, and dysrhythmia was observed in six cases; the minor complication rate in this study was 5%. In the ASD closure procedure performed by Diab et al.[18] in 15 infants, minor complications were reported in 3 cases and major complications in one case.

We have detected that most of the complications in patients who underwent angioplasty/stenting of aortic coarctation were local vascular complications, and all of them were considered minor complications. In a study by Ergül et al.[19], in 80 patients who underwent balloon angioplasty for coarctation of the aorta, it was reported that femoral artery occlusion occurred in 7.5% of the patients.

In cases of aortic valvuloplasty, the complication ratio was 32.6% and the major complication ratio was 2.2%. In the series of Mehta et al.[6], these ratios were 30% and 9%, respectively; in the series of Vitiello et al.[8], it was reported as 42% and 15%, respectively.

Local vascular complications constituted about half of all complications. All port site complications were minor complications and did not pose a serious problem, however, they cause problems such as prolonged hospitalization, extra medication, and transfusion. In the study of Vitiello et al.[8], arterial thrombosis was observed approximately 30% of all complications. In the study by Mehta et al.[6], the ratio of vascular complications was 32%. Vascular problems have an important place in other studies as well.

We have reported that the ratio of absent/weak pulses was higher in interventional procedures. In other studies, the incidence of thrombosis was reported to be higher in interventional procedures.[6,8] In our practice, a significantly higher rate of thrombosis was detected in cases of angioplasty/stenting of aortic coarctation and valvuloplasty, and this situation is also related to the arterial entry site.

Although local vascular complications were quite common in our study, the fact that most them improved only with anticoagulant treatment indicates that the cases were mild.

Device embolization occurred in 1.4% of the cases in our study. Device embolization rates were 4% in the study by Vitiello et al.[8] and 2.3% in the study by Mehta et al.[6] In our study, the rate of surgical removal of the embolized device in ASD closure was 2.3%. In the study of Chessa et al.[20], in which 417 ASD closure procedures were evaluated, this rate was 1.7%.

In the study by Szkutnik et al.[21], in which 11 VSD closure procedures were evaluated, device embolization occurred in 3 cases. In our study, 3 device embolizations were detected in 12 VSD closure procedures, and none of them required surgery.

The most common neurological complications in CCs are stroke and seizures.[22] In our practice, neurological complications were observed in 1.2%. In the study by Mehta et al.[6], the cerebral infarction rate was reported as 0.1%. Our ratio was 0.2%. In the literature, thromboembolism, intracranial hemorrhage, air embolism, drug reaction, and transient cerebral hypoperfusion are listed as causes of neurological complications.[8,23]

For neurological event development; young age, long procedure time, and invasiveness of the procedure have been reported as risk factors.[24]

Dysrhythmia was observed at a rate of 1%. In the study of Mehta et al.[6], the ratio of dysrhythmia was 1.8%. In the study of Vitiello et al.[8], it was 2.6% and it was the second most common complication. Huang et al.[13] reported the dysrhythmia rate as 9.1%.

Only one case of large vessel injury (0.13%) was reported in our practice. A wide muscular VSD closure procedure was planned in one-month-old patient, the procedure was terminated due to a vena cava inferior injury during the procedure and the patient was taken to surgery. No cases of cardiac perforation were found in our study. Myocardial/vascular injury, cardiac perforation, and tamponade were observed in 0.8% of cases in Vitiello et al.'s[8] study and 0.3% in Mehta et al.'s[6] study. Shen et al.[25] (n=23319) found the rate of cardiac perforation or tamponade to be 0.1%.

CONCLUSION

Our study's success and complication rates were similar to other studies. complications of cardiac catheterizations depend on the severity of the underlying CHD and the type of procedure.

Ethics

Ethics Committee Approval: This study was approved by the İstanbul University, İstanbul Faculty of Medicine Ethics Committee (2011-982-587).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Z.Y.A., Ü.A., Design: Z.Y.A., Ü.A., K.N., Data Collection or Processing: Z.Y.A., Ü.A., K.N., A.D., R.E., Analysis or Interpretation: Z.Y.A., Ü.A., Literature Search: Z.Y.A., Ü.A., Writing: Z.Y.A.

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Original Article

Late-effects of Chemoradiotherapy on Growth and Puberty in Survivors of Childhood Acute Lymphoblastic Leukemia

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ABSTRACT

Objective: The survival rate of childhood leukemia has reached 80% with evolving treatment modalities over the last 30 years, which is followed by an increased incidence of treatment-related long-term side effects. This study, it was aimed to evaluate the endocrine late effects of chemoradiotherapy in childhood acute lymphoblastic leukemia (ALL).

Methods: Forty-eight patients with ALL treated at the University of Health Sciences Türkiye, İstanbul Kanuni Sultan Süleyman Training and Research Hospital, Clinic of Pediatric Hematology and Oncology between 1997 and 2007 with at least 5-year follow-up after the chemotherapy, were included.

Results: Endocrine side effects were detected in 48% (n=23) of the cases. The most common endocrine side effect was short stature in the group treated with cranial radiotherapy (CRT), and obesity in the group that did not receive CRT. The median height standard deviation score (SDS) of the subjects who reached the final height (FH) was significantly lower [-1.44 (-2.1)-(-0.53)] compared with the median height SDS of the subjects who did not reach the FH [-0.24 (-1.23)-(0.6)]. There was a positive correlation between height SDS and IGF1 SDS, IGFBP3 SDS, body mass index SDS, and advanced bone age in subjects who did not reach FH (r=0.511, p=0.018, r=0.530, p=0.014, r=0.499, p=0.021, r=0.599, p=0.08, respectively). Precocious puberty was found in one patient who received CRT, and hypergonadotropic hypogonadism was found in one patient who did not receive CRT. Twenty-three percent of the group received CRT and 35% of the group who did not receive CRT had overweight/obesity. Central hypothyroidism was detected in one case and subclinical hypothyroidism was detected in two cases.

Conclusion: Long-term endocrine side effects were observed in approximately half of the cases with childhood ALL. Children treated with chemoradiotherapy should have regular endocrine system evaluation and growth monitoring starting from the diagnosis until the growth is completed.

Keywords: Acute lymphoblastic leukemia, growth, late effects, puberty, obesity

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INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common childhood cancer. With the developments in the diagnosis and treatment over the last 50 years, the survival rate of children diagnosed with ALL has increased significantly. With the combined use of chemotherapy (CT), central nervous system prophylaxis, and supportive treatment, the 5-year disease-free survival rate has reached 85% and the overall survival rate has reached 90%.

Improvements in survival have increased the importance of treatment-related long-term morbidity and mortality. Treatment-related chronic complications were reported in 62.3% of survivors of childhood ALL and significant endocrine-related complications were reported in 40% of them.[1] The most common endocrine-related complications have been reported as short stature, deficiency of growth hormone (GH), obesity/overweight, and precocious puberty.[2] GH deficiency after CRT is dose-dependent and mostly seen at a dose of 24 Gray (Gy); however, it can also be seen at doses as low as 18 Gy, or a single dose of 10 Gy applied during total body irradiation.[3] A decline in height growth is frequent during ALL treatment, particularly during the first year of treatment, but it can persist over time compromising patients' final height (FH).[4] Therefore, early diagnosis of endocrine disorders is essential to improve the quality of life. Furthermore, comprehending the underlying mechanisms is critical for establishing safer treatment protocols and appropriate follow-up plans to ensure the long-term health of survivors.[5]

Several studies have evaluated the effect of CT and prophylactic cranial radiotherapy (CRT) on growth and puberty in childhood ALL, however, results are conflicting. The mechanisms underlying these long-term endocrine effects remain unclear.

In this study, we studied the effects of CT and CRT on growth and puberty by evaluating the long-term follow-up data of children treated with ALL.

MATERIALS AND METHODS

A total of 48 cases, consisting of 22 boys (46%) and 26 girls (54%), who were treated with ALL in Pediatric Hematology and Oncology Clinic at the Ministry of Health Kanuni Sultan Süleyman Training and Research Hospital, between 1997 and 2007 were evaluated retrospectively. Ethics Committee approval was obtained from University of Health Sciences Türkiye, İstanbul Kanuni Sultan Süleyman Training and Research Hospital (date: 05.10.2012, approval no: 315) in accordance with the Declaration of Helsinki. Families and patients were informed about the study, and all subjects or their legal guardians provided written consent.

Inclusion Criteria:

1. The patient's and family's consent for the tests and examination,

2. Patients who have completed at least 5 years after the completion of treatment.

Exclusion criteria:

1. Patients for whom parental consent is missing,

2. Central nervous system involvement,

3. Presence of secondary malignancy,

4. Past spinal irradiation.

The following CRT protocol was applied to the CRT group;

Prophylactic CRT:

SRG (standard risk group): Not applicable

MRG (medium risk group): <1 year old: Not applicable

>1 - <2 years old: 12 Gy in T ALL only, not applicable in others.

≥ 2 years old: 12 Gy

HRG (highrisk group): >1 - <2 years old: 12 Gy

≥ 2 years old: 18 Gy.

In the case of CNS (central nervous system) involvement:

<1 year old: Not applicable

>1 - <2 years old: 12 Gy

≥ 2 years old: 18 Gy.

Follow-up Protocol

Evaluation of growth

For all subjects, information including age, gender, height, weight, parents' heights, target height (TH), age at diagnosis, treatment protocols (CT, CT+radiotherapy), puberty stage, and bone age was obtained. Thyroid-stimulating hormone (TSH), free T4 (fT4), luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol or testosterone, insulin-like growth factor-1 (IGF-1), IGF-binding protein-3 (IGFBP-3) were measured using standard techniques.

The heights of the patients and their parents were measured by the same person at three-month intervals with the "Harpenden Stadiometer". The growth velocity was monitored for one year. Body weight was measured using scales sensitive to 100 g. Body mass index (BMI) was calculated as weight/height squared (kg/m^2). The standard deviation score (SDS) was calculated for the height and body weight of the patients according to the standards of Turkish children.[6] Values between +2 SDS and -2 SDS for height were considered normal. Cases with a BMI percentile greater than or equal to the 95th percentile for age and sex were considered obese and those with BMI percentile between >85th and 95th percentile for age and sex were considered overweight.[7] The annual growth rate of each case was evaluated. Those with a growth rate of <4.5 cm/year were considered as having insufficient growth. TH was calculated using the formula: [father's height + mother's height]/2±6.5 cm for males and females, respectively. Left hand and wrist radiographs were taken in the anteroposterior position and the bone age was assessed by a single observer using the Greulich and Pyle method.[8] Bone age difference (BAD)>+1-

year-old is defined as the advancement of bone age, and BAD<-1 year old is defined as a retardation of bone age. GH stimulation test was performed using clonidine in patients with insufficient growth rate and a retarded bone age. In patients with GH peak value <10 ng/mL in the first GH stimulation test, the second GH stimulation test was performed using L-dopa.

Serum IGF-1 and IGFBP-3 levels were measured with the chemiluminescence method (Immulyte 2000 R Siemens). SDS were calculated for IGF-1 and IGFBP-3. Values between +2 SDS and -2 SDS were accepted as normal.[9]

Evaluation of puberty

Pubertal development was performed according to the Tanner stage.[10] Delayed puberty was defined as the absence of breast development by the age of 13 in girls, and testicular weight <4 mL was measured by Prader orchiometry by the age of 14 in boys.

The thyroid functions of the patients were evaluated by measuring fT4 and TSH values. Increased serum TSH with low fT4 was defined as clinical hypothyroidism. Increased serum TSH with normal fT4 was defined as subclinical hypothyroidism.

Statistical Analysis

In this study, statistical analyzes were performed with NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA) package program.

In addition to descriptive statistical methods (mean, standard deviation), the Independent t-test was used in the comparison of the paired groups, and the chi-square and Fisher's exact test were used in the comparison of the qualitative data. Normally distributed continuous variables were given using the mean and standard deviation, and skewed continuous variables were given using the median and 25-75 percentiles. The Spearman's rank correlation test was used to analyze the association between the height SDS and the IGF1 SDS, IGFBP3 SDS, BMI SDS, and bone age progression in subjects who did not reach FH. The results were evaluated at a significance level of $p<0.05$.

RESULTS

The mean age at ALL diagnosis was 4.7±1.2 years and the mean age at the time of the study was 14.3±2.8 with an average follow-up duration of 9.7±1.9 years after CRT. All patients received the CT protocol, sixty-four percent (n=31) of the cases received CRT and thirty-six percent (n=17) of the patients did not receive CRT. The clinical and biochemical features of the cases are summarized in Table 1.

Endocrine system pathology was detected in 47.9% (n=23) of the cases at the time of the study. The most common endocrine pathology was short stature in the group of patients who received CRT, whereas obesity was the most common condition in the group who did not receive CRT.

Evaluation of growth

The median height SDS of the subjects at the final control was -0,48 [(-1.8)-(-0.1)] (Table 1), the TH SDS was -0.7 [(-1.38)-(0.01)], and the TH matches (TH SDS-height SDS) were -0.02 [(-0.9)-(0.6)]. Fifty-six percent (n=27) of the cases reached the FH. The median height SDS of the subjects who reached the FH was -1.44 [(-2.1)-(-0.53)], and among those subjects, 29.6% (n=8) had a FH below -2 SDS (Table 2). The median height SDS of the subjects who did not reach the FH was -0.24 [(-1.23)-(0.6)] and among those subjects, 14% (n=3) had a FH below -2 SDS. A significant difference in the height SDS was found between these two groups (p=0.022). There was no difference in the height SDS, TH SDS, and TH compliance between the groups who received CRT (n=31) and those who did not (n=17). The median IGF1 SDS value of all cases was 0.41 [(-0.37)-(1.3)], IGFBP3 SDS value was -0.4 [(-1.1)-(-0.18)]. IGF1 and IGFBP3 were lower in the group who received CRT compared with the group who did not (p=0.036, p=0.027) (Table 2). Eight of the nine patients with short stature (height SDS <-2) received CRT and two had GH deficiency.

The median FH SDS of 27 cases reaching FH is -1.44 [(-2.1)-(0.53)], FH/TH match (TH SDS-FH SDS) is 0.06 [(-0.17)- (1.1)] SDS. While the FH SDS of the patients who received CRT and those who did not receive CRT were similar (p>0.05), the difference between the TH SDS and the FH SDS values was higher in the CRT group (p=0.018). Thirty-three percent (n=7) of the patients who received CRT had a FH below -2 SDS, 28.6% (n=6) could not reach the TH, and all the patients who did not receive CRT were detected to have a FH consistent with the TH (Table 2).

There was a positive correlation between the height SDS and the IGF1 SDS, IGFBP3 SDS, BMI SDS, and bone age progression in subjects who did not reach FH (r=0.511, p=0.018, r=0.530, p=0.014, r=0.499, p=0.021, r=0.599, p=0.08) (Figure 1). A positive correlation (r=0.518, p=0.006) was observed between height SDS and TH SDS in subjects who reached the FH.

Evaluation of puberty

At the end of the study, 94% of the cases were pubertal. In the CRT group, a girl was diagnosed with precocious puberty, and Gonadotrophin releasing hormone (GnRH) analog therapy was given. In one patient in the group who did not receive CRT, despite the pubertal progress was initially appropriate for his age, hypergonadotropic hypogonadism developed during the follow-up. The pubertal findings and gonadotropin levels of all other cases were compatible with their age.

Obesity/Overweight

At the end of the study, the median body mass index (BMI) SDS of all cases was 0.88 [(0.15)-(1.66)]. Fourteen percent (n=7) of the cases had obesity and 13% (n=6) of the cases were overweight. The BMI SDS was similar between the group that received CRT and the group who did not receive CRT. Twenty-three percent of the group received CRT and 35% of the group who did not receive CRT were found to be obese or overweight. In the group who did not reach the FH, a positive correlation was found between BMI SDS and advanced bone age (r=0.555, p=0.009).

Table 1. Clinical and laboratory characteristics of the patients who received and did not receive CRT				
	Total (n=48)	**CRT (n=31)**	**CT (n=17)**	**p-value**
Age (years)	14.3±2.8	14.9±2.8	12.2±1.7	0.013
Gender (M/F)	22/26	16/15	6/11	0.037
Age of diagnosis (years)	4.67±1.23	4.38±1.1	4.72±1.4	
Height (SDS)	-0.48 [(-1.8)-(-0.1)]	-0.5 [(-2.02)-(0.1)]	-0.33 [(-1.05)-(0.13)]	0.306
BMI (SDS)	0.88 [(0.15)-(1.66)]	0,86 [(-0.2)-(1.32)]	1,05 [(0.3)-(1.9)]	0.291
Puberty % (n) Prepubertal Stage 2 Stage 3 Stage 4 Stage 5	 6.3 (n=3) 10.4 (n=7) 10.4 (n=7) 31.3 (n=15) 33.3 (n=16)	 3.2 (n=1) 12.9 (n=4) 9.7 (n=3) 29 (n=9) 45.2 (n=14)	 11.8 (n=2) 17.6 (n=3) 23.5 (n=4) 35.3 (n=11.8) 11.8 (n=2)	0.057
Endocrinologic pathology (%) Short stature GH deficiency Precocious puberty Obesity/Overweight Hypogonadism Hypothyroidism	47.9 (n=23) 18.7 (n=9) 4.1 (n=2) 2 (n=1) 27.1 (n=13) 2 (n=1) 6.2 (n=3)	48.4 (n=15) 25.8 (n=8) 6.4 (n=2) 3.2 (n=1) 22.6 (n=7) 0 6.4 (n=2)	47.1 (n=8) 5.9 (n=1) 0 0 35.3 (n=6) 5.8 (n=1) 5.8 (n=1)	
BMI: Body mass index, CRT: Cranial radiotherapy, CT: Chemotherapy, GH: Growth hormone, SDS: Standard deviation score				

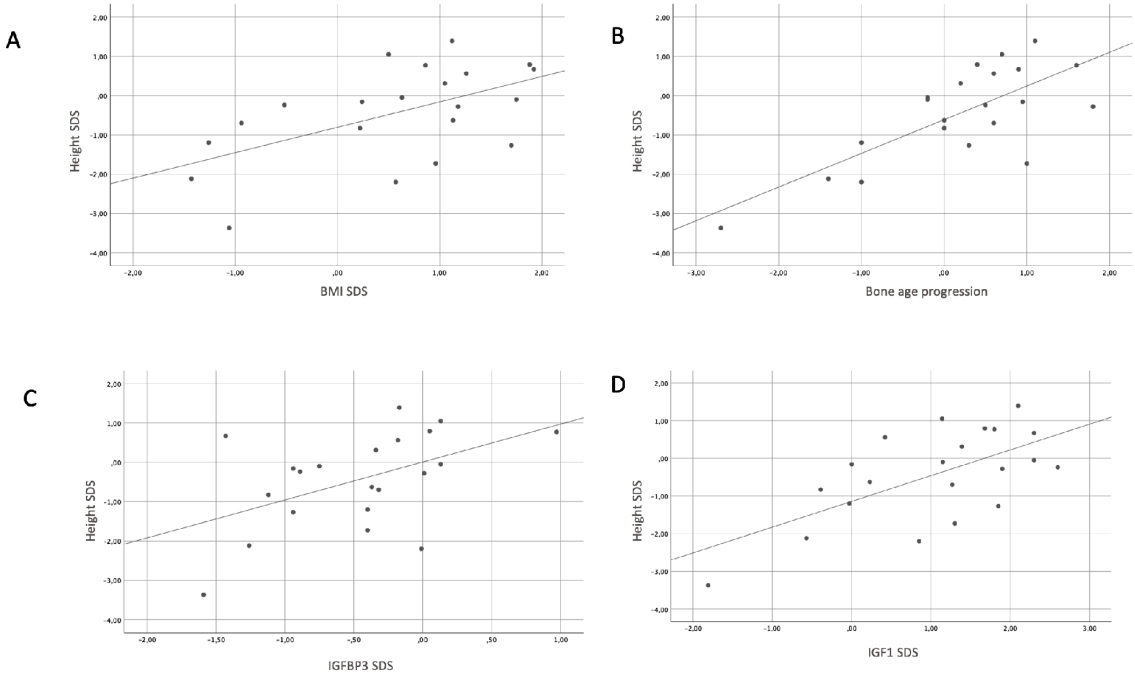

Figure 1. Correlation of factors influencing height SDS in cases who did not reach final height.

A) Correlation between height SDS and BMI SDS (r=0.499, p=0.021). B) Correlation between height SDS and bone age progression (r=0.599, p=0.08). C) Correlation between height SDS and IGFBP3 SDS (r=0.530, p=0.014). D) Correlation between height SDS and IGFBP3 SDS (r=0.511, p=0.018)

SDS: Standard deviation score, BMI: Body mass index, IGFBP3: insulin-like growth factor binding protein-3

Table 2. Laboratory characteristics of the patients who received and did not receive CRT

	Total (n=48)	CRT (n=31)	CT (n=17)	p-value
Bone age (years)	15 (12.5-17)	15.5 (13-18)	13 (12-14.5)	0.01
TH (SDS)	-0.7 [(-1.38)-(0.01)]	-0.71 [(-1.4)-(0.01)]	-0.61 [(-1.15)-(0.05)]	0.71
TH-height (SDS)	-0.02 [(-0.9)-(0.6)]	0.11 [(-0.94)-(0.75)]	-0.27 [(-1.07)-(0.6)]	0.438
Compatibility with the target % (n)	85.4 (n=41)	83.8 (n=26)	88.2 (n=15)	0.5
TSH (μIU/mL)	1.8 (1.4-4.2)	1.84 (1.5-2.2)	1.71 (1.26-2.31)	0.407
fT4 (ng/dL)	0.9 (0.8-1)	0.9 (0.8-1)	0.9 (0.77-1)	0.957
LH (mIU/mL)	3.55 (0.7-4.7)	3.1 (0.57-4.4)	3.79 (0.71-5.1)	0.539
FSH (mIU/mL)	4.3 (1.95-6.15)	4.2 (1.6-5.8)	5.4 (2.1-7.7)	0.414
IGF1	360.5 (260-413.7)	321 (249-412)	408 (312-415)	0.101
IGF1SDS	0.41 [(-0.37)-(1.3)]	0.03 [(-0.76)-(1.22)]	0.86 [(0.17)-(1.78)]	0.036
IGFBP3	4549 (3717-5097)	4370 (3500-5051)	4800 (4100-5160)	0.14
IGFBP3SDS	-0.4 [(-1.1)-(-0.18)]	-0.7 [(-1.23)-(-0.32)]	-0.3 [(-0.74)-(0.03)]	0.027
FH % (n)	56.3% (n=27)	67.7 (n=21)	35.3 (n=6)	0.03
FH SDS (%)	-1.44 [(-2.1)-(-0.53)]	-1.5 [(-2.15)-(-0.42)]	-0.98 [(-2.1)-(-0.3)]	0.04
FH SDS <-2 (%)	29.6% (n=8)	33.3% (n=7)	16.6% (n=1)	
TH -final height (SDS)	0.06 [(-0.17)-(1.1)]	0.55 [(-0.07)-(1.52)]	-0.19 [(-0.5)-(0.0)]	0.018
Case reaching the target in the final length % (n)	77.7 (21/27)	71.4 (15/21)	100 (n=6/6)	

CRT: Cranial radiotherapy, CT: Chemotherapy, FH: Final height, fT4: FreeT4, FSH: Follicle stimulating hormone, IGF-1: Insulin-like growth factor-1, IGFBP3: Insulin-like growth factor-binding protein 3, LH: Luteinizing hormone, SDS: Standard deviation score, TH: Targeted height, TSH: Thyroid stimulating hormone

Hypothyroidism

A subject who received CRT at an early age (2 years old) was diagnosed with central hypothyroidism with low fT4 and TSH and GH deficiency. In two cases diagnosed with subclinical hypothyroidism with mild TSH elevation (9.1 μIU/mL) and normal fT4 level, TSH elevation persisted during follow-up. LT4 replacement therapy was initiated in all three cases.

DISCUSSION

In our study, long-term follow-up data of 48 patients who were treated for childhood ALL and the long-term effects of chemoradiotherapy on growth and pubertal development were evaluated. It was shown that late effects related to the endocrine system were present in approximately half of the cases. The most common endocrine disturbances were growth retardation and obesity or overweight. CRT was associated with a loss in FH.

It has been reported that growth retardation/stagnation is frequently seen during childhood ALL treatment, but up to 70% of the cases would have a catch-up growth within the following 2 to 3 years after the end of treatment.[11] In contrast, others demonstrated that growth retardation persists with a loss in final adult height.[4,5,12,13] In our study, short stature was detected in 14% of the patients who did not reach the FH and in 30% of those who did reach FH.

The mechanism of action of CT and prophylactic CRT on the growth remains unclear. Regression in growth and loss of height is most evident in the first year of induction and continuation treatment. It has been reported that catabolic effects are observed during this acute period. Furthermore, CT agents and corticosteroids cause growth retardation due to the reduction of GH, IGF-1 levels, and IGF-1 tissue sensitivity.[14-17] However, the side effects of on growth are usually temporary. Although a significant decrease in height SDS was observed in these cases during the treatment, it has been shown that growth is often achieved after cessation of the treatment and patients reach a normal adult height with a minimal loss.[5,18] It has been reported that 31-48% of patients who received CRT have a FH loss of approximately 10 cm.[19] In another study, 71% of cases had a decrease in height of more than 1 SDS six years after the treatment. In our study, short stature was present in 22.8% (n=11) of the cases, and except for one case, all received CRT. Although the height SDSs were similar between the group of patients who received CRT and the group who did not, while their growth continued; we observed that the FH SDS of those who received CRT was lower and their Parental TH compatibility was worse. Similar to previous studies, it was concluded that the negative effects of CRT on growth continued until growth was completed.

The fundamental mechanism causing the negative effect of cranial RT on growth was proposed to be GH deficiency caused by damage to the hypothalamus.[20] This effect is dose-dependent and is usually seen at a dose of 24 Gy. However, recent data revealed that subjects who received 18 Gy CRT had a significant height loss in a 3-year follow-up compared with those who received 12 Gy CRT.[21] CRT exposure at an early age (<5 years old) has been reported as a risk factor for GH deficiency.[12,19] However, GH deficiency may not

always explain the short stature seen after CRT.[22,23] In our study, IGF1 SDS and IGFBP3 SDS were found to be significantly lower in patients who received CRT than those who did not receive CRT. Likewise, most of the patients with short stature received CRT at an early age, suggesting that GH deficiency developed secondary to CRT. However, in our cohort, only two of 11 patients with short stature were diagnosed with GH deficiency. This suggests that additional factors affecting growth should be considered in ALL.

CRT can also affect growth by changing the timing of puberty. It has been shown that CRT increases the risk of early puberty, particularly in girls diagnosed with ALL and in patients diagnosed at an early age.[13,18,23] In early puberty, growth and bone maturation are accelerated. Lack of adequate pubertal growth spurt and premature closure of epiphyseal plates result in decreased FH. Although early puberty was detected in only one of our cases, there was a high rate of short stature. It has been reported that although puberty starts at a normal time, CRT may cause height loss by disrupting the pubertal growth spurt without affecting the timing of the puberty.[24] According to a study in which the cases were followed from the time of diagnosis until the FH, it was found that the patients initially grew adequately after the completion of the treatment; however, by the age of 14 for boys and by the age of 11 for girls, a significant decrease in height SDS and a loss of -1.5 SDS in FH was observed.[4]

All of our cases were followed up for at least 5 years after the end of the treatment. The height SDS values of the cases who continued to grow were found to be significantly higher than those who were treated similarly and reached the FH. Additionally, in the growing group, advanced bone age was closely related to the height SDS. These results strongly suggest that although the pubertal timing is not effected, the course of the pubertal process is impaired in patients who received ALL treatment. Although the height SDS remains normal during the growth period, the final adult height may be compromised.

Conflicting results were obtained in the studies evaluating the effect of childhood ALL on obesity and overweight.[25,26] The prevalence of obesity in adults who received treatment for ALL has been reported to be 11-56%.[27,28] In our study, the rate of obese or overweight was high (27.2%) and there was no difference between the groups who received CRT and those who did not receive CRT. There was a positive correlation between BMI SDS and advanced bone age in cases that continued to growing. This suggests that obesity, which is common in patients who received ALL treatment, may be a factor that adversely affect the final length.

Study Limtations

The fundamental limitation of our study was that comparisons between small and heterogeneous subgroups were not statistically possible. Another limitation was that the cause-effect relationship could not be fully elucidated due to the inability to evaluate the growth patterns of the cases given the cross-sectional design of the study.

CONCLUSION

Especially in patients who received CRT, although the height SDS remained normal and parental TH compatibility was optimal during the growth period, there are loss in FH, higher rate of short stature, and parental TH incompatibility. Our findings suggest that advanced bone age causes loss of FH even in cases without precocious puberty. To elucidate the cause-and-effect relationship of these late negative effects of ALL treatment on growth, there is a need for prospective studies in which the pubertal course, growth pattern, and bone age are monitored from the time of diagnosis to the completion of growth.

Ethics

Ethics Committee Approval: Ethics Committee approval was obtained from University of Health Sciences Türkiye, İstanbul Kanuni Sultan Süleyman Training and Research Hospital (date: 05.10.2012, approval no: 315) in accordance with the Declaration of Helsinki.

Informed Consent: Families and patients were informed about the study, and all subjects or their legal guardians provided written consent.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.B.E., A.A., M.E., T.A., Z.Ş., G.A., Concept: S.B.E., A.A., M.E., Z.Ş., G.A., Design: S.B.E., A.A., E.B., T.A., G.A., Data Collection or Processing: S.B.E., E.B., M.E., G.A., Analysis or Interpretation: S.B.E., A.A., E.B., T.A., G.A., Literature Search: S.B.E., A.A., E.B., M.E., Writing: S.B.E., A.A., E.B., G.A.

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Case Report

The Importance of Thyroid Function Tests in a Patient Presenting with Precocious Menarche: Van Wyk Grumbach Syndrome

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ABSTRACT

Van Wyk Grumbach syndrome (VWGS) is characterized by untreated severe hypothyroidism, isosexual precocious puberty, multiple ovarian cysts and delayed bone age. Although it is extremely rare, it is important to recognize before the unnecessary ovarian surgeries because of its curability with a simple thyroid hormone replacement. Here, we reported a 5-year-and-3-months old female patient presented with precocious menarche and diagnosed as VWGS with primary hypothyroidism, isosexual precocious puberty and multiple ovarian cysts. Following L-thyroxine replacement therapy, all complaints and hormonal abnormalities resolved and finally, the multicystic mass structure in the ovaries disappeared completely. The diagnosis of VWGS should be kept in mind because simple L-thyroxine replacement completely resolves symptoms and abnormalities and prevents unnecessary investigations for malignancies and surgeries.

Keywords: Van Wyk Grumbach syndrome, hypothyroidism, precocious puberty

INTRODUCTION

Van Wyk Grumbach syndrome (VWGS) is characterized by untreated severe hypothyroidism, isosexual precocious puberty, multiple ovarian cysts and delayed bone age.[1] All the features can be resolved with treatment of the hypothyroidism. Girls mostly present with classic hypothyroid symptoms, delayed growth, breast development and precocious uterine bleeding without pubic or axillary hair. Rarely, this syndrome can also be seen in boys. Boys with this syndrome have the only symptom of macro-orchidism.[2,3] Laboratory evaluation reveals low free thyroxine (T4) with elevated Thyroid-stimulating hormone (TSH), prolactin and estradiol. Gonadal enlargement and multiple ovarian cysts or mass can be detected in radiological evaluations, and therefore, malignant disease of the ovary is often suspected.

The disorder is most likely due to complex interactions of the hormonal axis; (1) excess TSH stimulates the follicle stimulating hormone (FSH)-receptor (FSHR), (2) pituitary hyperplasia and hyperstimulation, (3) secondary ovarian hyperstimulation.[1,4] Although the syndrome is extremely rare, it is important to recognize before the unnecessary ovarian surgeries because of its curability with a simple thyroid hormone replacement. In this study, we reported a case presented with precocious menarche and diagnosed as VWGS with primary hypothyroidism, isosexual precocious puberty and multiple ovarian cysts.

CASE REPORT

A 5-year-and-3-month-old female was presented with menarche. There was no history of trauma or bleeding disorders. Her parents reported fatigue, constipation, intolerance to cold and

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lack of appetite. She was born as the first child of healthy non-consanguineous parents and delivered at term by normal vaginal delivery after uneventful pregnancy. In family history, the mother was diagnosed with Hashimato's thyroiditis. There was no family history of precocious puberty. Her past medical history revealed that she had adenotonsillectomy at three years old. On physical examination, weight was 18.5 kg [-0.1 standard deviation score (SDS)], height was 105 cm (-1.1 SDS). She was lethargic and pale. She had puffiness of face, dry brittle hair, depressed nasal bridge and short fingers. Her breast development was Tanner stage 2 without axillary or pubic hair. She had no goiter. Other systemic physical examination features were unremarkable (Figure 1).

Initial laboratory investigations revealed normal electrolytes and liver-kidney functions. She had macrocytic anemia with a hemoglobin level of 9.7 g/dL (N, 10.2-12.7). Hormonal evaluation revealed TSH level was greater than 100 mIU/mL (N, 0.7-5.97), free T4 was 0.112 ng/dl (N,0.96-1.77), creatin kinase was 490 U/L (N, 0-170), FSH was 6.3 mIU/mL (N, 0-4), luteinizing hormone (LH) was < 0.1 mIU/mL (N, <0.2), estradiol was 34.41 ng/dL (N, <20), prolactin was 61.4 ng/mL (N, 4.79-23.3) (Table 1). Contrary with the pubertal development, her bone age was delayed and compatible with 3 years and 6 months according to The Greulich and Pyle atlas (Figure 1). On examination for hypothyroidism, anti-thyroid peroxidase antibody was more than 600 IU/mL (N, 0-34), anti-thyroglobulin antibody was >4000 IU/mL (N, 0-115), ultrasonographic examination of the thyroid revealed thyroiditis with enlargement of the thyroid volume. Ultrasonography (USG) of the pelvis revealed pubertal uterus (41x20x25 mm) with an endometrial thickness of 7 mm, enlarged left ovary with multiple follicles, and multi-cystic mass with a size of 42x24x30 mm in the right ovary location, with a thick-walled multi-septum without significant blood supply. Pelvic magnetic resonance imaging confirmed findings of the pelvic USG. Tumor markers including AFP, LDH, β-hCG were normal. In summary, with the findings of severe hypothyroidism, isosexual precocious puberty with delayed bone age and massive ovarian cysts, a diagnosis of VWGS was considered and then low-dose L-thyroxin treatment was started and gradually increased to 50 mcg, the dose at which euthyroidism was finally achieved. Following L-T4 replacement therapy, all complaints and hormonal abnormalities resolved and finally, the multi-cystic mass structure in the ovaries disappeared completely.

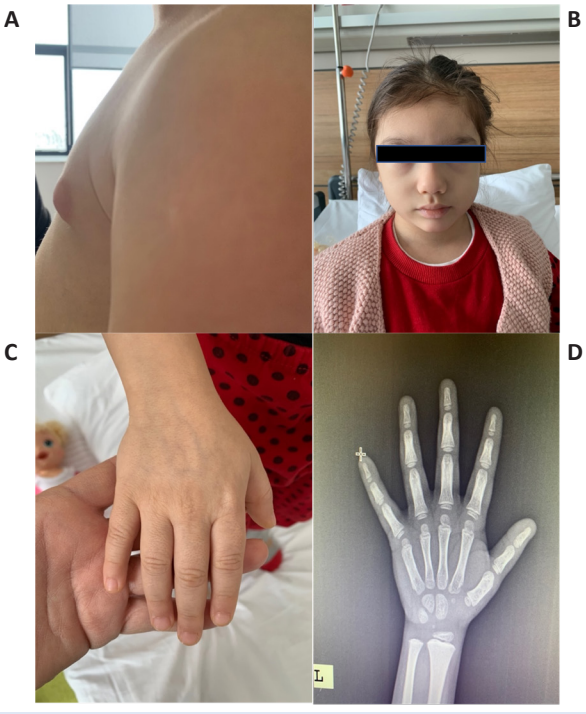

Figure 1. Clinical characteristics (A-C) and the X-ray of the patient's left hand showing delayed bone age (D)

Written informed consent was obtained from the patient and her parents for the publication of this case report and any accompanying images.

DISCUSSION

The typical manifestation of untreated hypothyroidism is failure to grow and sexual development with delayed bone age. In this study, we reported a case of VWGS, an unusual presentation of hypothyroidism who was presented with precocious menarche and multi-cystic ovaries.

VWGS is first reported in 1905 by Kendle[5] in a patient presenting with a typical cretin appearance and remarkable precocious puberty. She had menstruation at 5 years and 2-month age. Moreover, she had not menstruate since she resumed the thyroid extract. But the syndrome coin the term of VWGS in 1960 by Wyk and Grumbach[1] with a report about three girls with untreated hypothyroidism, myxedema, precocious menstruation, breast development and galactorrhea without pubic and axillary hair. Since then, many case reports published about this syndrome with varying presentations.

The mechanism of the syndrome remains unclear. Excess TSH levels, act directly on FSH receptors to induce ovarian hyperstimulation and the degree of the sexual development may be related to the severity of TSH elevation.[6] An *in vitro* study has been shown that TSH exhibit a dose-dependent cAMP response at the human FSHR to stimulate adenylyl cyclase activity and excess TSH can show FSH-like activity.[6] Ryan et al.[4] investigated *FSHR* variant in terms of increased sensitivity of human FSHR to TSH in eight patients exhibited hypothyroidism and gonadal hyperstimulation, but associated variant was not found.

The disease usually presents with breast development, vaginal bleeding or multi-cystic ovaries and rarely with galactorrhea. The precocious puberty is always isosexual in cases of VWGS. The serum gonadotropin levels are prepubertal in all reported cases. The presence of precocious puberty and ovarian cysts suggests an estrogen-secreting ovarian tumor.[7-10] But if the patient is hypothyroid and bone age is delayed, it is crucial to recognize the clinical and imaging features of VWGS, to avoid

Table 1. Clinical and laboratory characteristics of the patient

	At diagnosis	At follow-up	At follow-up	Normal range
Age	**5 years and 2 months**	**5 years and 4 months**	**5 years and 7 months**	
Weight Z-score	-0.1	-0.6	-0.8	
Height Z-score	-1.1	-0.7	0.1	
BMI Z-score	0.8	-0.1	-1.3	
Hemoglobin (g/dL)	9.7	10.1	11.3	10.2-12.7
MCV (fL)	90.4	90	77.2	72.3-85
TSH (mIU/mL)	>100	1.81	1.58	0.7-5.97
FT4 (ng/dL)	0.11	1.46	1.42	0.96-1.77
FSH (mIU/mL)	6.33	3.46	3.66	0-4
LH (mIU/mL)	<0.1	0.33	0.12	<0.1
Estradiol (pg/mL)	34.41	25.91	<5	<20
Prolactin (ng/mL)	61.4	16	16	4.7-23.3
Anti TPO (IU/mL)	>600	----	----	0-34
Anti TG (IU/mL)	>4000	----	----	0-115
CK (U/L)	490	50	47	0-170
AFP (ng/mL)	3.72	----	----	0-12
β-hCG (mIU/mL)	< 0.1	----	----	0-5.3

BMI: Body mass index, MCV: Mean corpuscular volume, TSH: Thyroid-stimulating hormone, FT4: Free thyroxine, FSH: Follicle stimulating hormone, LH: Luteinizing hormone, Anti-TPO: Anti-thyroid peroxidase antibody, Anti-TG: Anti-thyroglobulin antibody, CK: Creatine kinase, AFP: Alfa fetoprotein, β-hCG: Beta-human chorionic gonadotropin

unnecessary surgeries.[10] For this purpose, Browne et al.[10] reported the clinical and imaging findings of five hypothyroid cases. Two of these reported cases presented with precocious menarche and were diagnosed VWGS; bilateral multi-cystic enlarged ovaries were present and regressed between 3 months and 1 year after the treatment. Other two of the cases were post pubertal and diagnosed as hypothyroidism before but they were non-compliant with T4 replacement; in these cases, the 6 and 5 cm ovarian cysts were regressed with recommencement of thyroid hormone therapy. The fifth case was 17 years at age and presented with oligomenorrhea; pelvic USG had revealed bilateral enlarged ovaries with multiple cysts; the largest was 3 cm in diameter. With T4 replacement ovaries had shrunk and cysts were dissolved. Because of this study, it was thought that cystic ovary enlargement occurred with the same mechanism in pre and post-pubertal cases. Therefore, thyroid function tests should be evaluated in all cases with ovarian multi-cystic enlargement. Surgery is usually unnecessary for ovarian cysts but torsion may develop in the enlarged ovary and surgery may only be required in this situation.[11] Usually, ovarian cysts resolve within 2-12 months. In some cases, tumor markers were found to be abnormal.[12] Our case also had multi-cystic ovaries at presentation with normal value of tumor markers and ovarian cysts resolved after 3 months of thyroid replacement.

Most reported cases of VWGS are prepubertal girls; however it can be rarely presented in males.[2] Thyroid hormone was shown to play a critical role in the Sertoli cell maturation and Leydig cell differentiation.[13] The effect of hypothyroidism on testis is proliferation of Sertoli cells and testicle enlargement without virilization.[3,11] Boys with this syndrome have the only symptom of macro-orchidism.[2,3,14]

In VWGS, the most common cause of hypothyroidism is autoimmune thyroiditis.[7,11] Likely, in our case positive thyroid antibodies and USG of the thyroid confirmed autoimmune thyroiditis.

Elevated prolactin levels, which is also detected in our case, and pituitary hyperplasia, which is caused by a decrease in the regulation of the feedback of thyroid hormones, were seen in almost all reported cases.[7,10] After replacement of thyroid hormone, pituitary enlargement regresses like the other abnormalities.[12]

Other unusual presentations or features may also accompany the syndrome. Baranowski and Högler[15] reported a girl with a streaky newly developed hyperpigmented skin lesion in axilla with parathormone depression and this was thought to be due to hormonal overlapping with TSH between melanocyte-stimulating hormone and parathormone. Razi et al.[16] reported a case of 9-year-old female presented with vaginal bleeding and difficulty in walking. On evaluation, she was found to be VWGS associated with Kocher Debre Semelaigne syndrome (KDSS). KDSS is another rare complication of untreated long-standing hypothyroidism and characterized by hypothyroidism, muscle pseudohypertrophy, elevated levels of creatine phosphokinase and myxedema. Similarly, our patient's creatine phosphokinase level was high, confirming the thyroid myopathy. Egodawaththe et al.[17] reported

another case of a 6-year-old girl presented with vaginal bleeding, markedly short stature and oligosyndactyly. As in our patient, macrocystic anemia is one of the frequently reported findings in these patients.[10,11,15]

CONCLUSION

In conclusion, the diagnosis of VWGS should be kept in mind because simple T4 replacement completely resolves symptoms and hormonal abnormalities and prevents unnecessary investigations for malignancies and surgeries. In this study, T4 replacement provided a resolution of the symptoms and reduction in ovarian size and cysts.

Ethics

Informed Consent: Written informed consent was obtained from the patient and her parents for the publication of this case report and any accompanying images.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ö.K., Concept: Ö.K., S.A., Design: Ö.K., S.A., Data Collection or Processing: Ö.K., Analysis or Interpretation: Ö.K., Literature Search: Ö.K., S.A., Writing: Ö.K., S.A.

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