Case Report / Olgu Sunumu

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A Diagnostic Dilemma: Job Syndrome Mimics Abusive Trauma

Bir Tanı İkilemi: Fiziksel İstismarı Taklit Eden Job Sendromu

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Abstract

In some cases, making of physical abuse diagnosis can be difficult if the findings were derived from an unusual disease or an unexpected finding of a common disease. A female infant was admitted to emergency department of our hospital, who was suffering from loss of consciousness. Examination and imaging methods revealed subarachnoid hemorrhage, old and new femur fractures, bilateral retinal hemorrhage. Performing genetic tests with multidisciplinary approach concluded that our case was found to have a mutation, DOCK8 (NM_001190458; c.2071G>A; p.Val691Met), suggests to Job syndrome (JS). JS is not only an immunodeficiency syndrome but also can be manifested by skeletal and connective tissue disorders. The fractures were most likely due to JS. Physicians must be aware of these probabilities. On the other hand, though it was only reported in a heterozygous form in GenomAD (genome aggregation database) it has big value that it was homozygous in our case.

Keywords: Child abuse, Job syndrome, physical abuse

Öz

Fiziksel istismar tanısı koymak, sık görülmeyen bir hastalığa ait bulguları ya da yaygın görülen bir hastalığın beklenmeyen bir bulgusunu içeriyorsa bazı olgularda zor olabilmektedir. Küçük bir kız bebek annesi tarafından hastanemizin acil servisine bilinç kaybı şikayetiyle getirilmiştir. Muayene ve görüntüleme tetkikleri subaraknoid kanama, yeni ve eski femur kırıkları, bilateral retinal kanamayı ortaya koymuştur. Multidisipliner yaklaşımla yapılan genetik testler sonucunda olgumuzun Job sendromu (JS) olduğunu ortaya koyan DOCK8 (NM_001190458; c.2071G>A; p.Val691Met) mutasyonuna sahip olduğu belirlendi. JS sadece bir immün yetmezlik sendromu olmayıp aynı zamanda iskelet ve bağ dokusu bozukluklarıyla da ortaya çıkabilmektedir. Kırıklar büyük olasılıkla JS'ye bağlıydı. Hekimlerin bu olasılıkların farkında olması gerekir. Öte tarafdan, daha önce sadece GenomAD'de (Genom Aggregation Database) heterozigot form rapor edilmesine karşın, olgumuzun homozigot formda olması oldukça değerlidir.

Anahtar Kelimeler: Çocuk istismarı, Job sendromu, fiziksel istismar

Introduction

The responsibility of the physicians involves conducting the physical examination, recording the findings, and ultimately preparing an expert report.[1] Physical abuse is a significant variety of childhood maltreatment. Physicians are legally and ethically obliged to identify child maltreatment to prevent further abuse. Either they treat their patients or widely investigate the symptoms for differential diagnosis. In many cases, making a physical abuse diagnosis can be difficult if it depends only on physical examination. Especially the patient with suspicion of physical abuse, suffers from an illness that has findings can make the physician's mind confuse. A wide variety of diseases can mimic abusive fracture findings, such as rickets, secondary hyperparathyroidism, osteoporosis, Menkes syndrome, leukemia, and hemophagocytic lymphohistiocytosis, in addition to birth and rescue traumas.[2]

Hyper-IgE syndrome, also known as Job syndrome (JS), is an immunodeficiency disease characterized by recurrent infections, high serum immunoglobulin E levels, staphylococcal abscess, eczema, and pulmonary tract infections.[3] JS is known as Hiob syndrome in Germany.[2] JS is heritable in two ways: Autosomal dominant and autosomal recessive (AR).[3] The

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OR form of JS can be manifested by dental, skeletal, and connective tissue disorders.[3] The AR form is quite rare; in fact, almost 200 cases have been reported.[3]

Aim of this case presentation was to draw attention to the importance of making a diagnosis of child physical abuse. Diagnosis of physical abuse is simply based on excluding irrelevant diseases. JS is one of the diseases that have findings mimicking a physical abuse as well as our case. On the other hand, the causes of physical child abuse and shaken baby syndrome should be considered.

Case Report

The case was a 5-month-old female infant who was admitted by her mother to the pediatric emergency department suffering from loss of consciousness. She was 5200 g, 68 cm in length, and 39 cm in head circumference. Examination and imaging revealed subarachnoid hemorrhage, old and new femur fractures, and bilateral retinal hemorrhage.

Her mother was 21 years old when she gave birth. Our case is the first pregnancy of her mother. She was born in 830 g via c-section. Her first Apgar score was 6 or 7. The patient was premature and small for gestational age. After birth, she suffered from pulmonary hemorrhage, icterus of the newborn, patent ductus arteriosus, Patent foramen ovale, and retinopathy of prematurity (ROP). When she was 3 months old, she was treated because of cellulite on the left thigh. At the age of 4 months, she developed a central nervous system infection.

Once the pediatricians who examined her were in doubt about physical abuse such as Shaken baby syndrome due to the findings above. The case was referred to each department of ophthalmology, orthopedics, medical genetics, and forensic medicine. Either detailed physical examination or laboratory tests (Table 1) and imaging methods were performed.

Table 1. Laboratory findings (3 months age*)

Parameter	Amount
Alkaline phosphatase	351 U/L
Phosphorus	5.53 mg/dL
Calcium	8.97 mg/dL
Potassium 25 hydroxy vit D	5.69 mg/dL 28.35 ng/mL
Free T3	4.09 pg/mL
Parathyroid hormone	55.17 ng/dL
Free T4	1.42 ng/dL
Thyroid-stimulating hormone C-reactive protein Eosinophil Neutrophil Lymphocytes White blood cells	4.94 uIU/mL 25.6 mg/L* 0.05* 1.77* 3.54 * 5.8 mcL*

X-ray revealed a fracture line in the distal part of the right femur and callus tissue, which is a sign of an old fracture in the distal region of the left femur (Figure 1a-c). Magnetic resonance imaging of the brain revealed a common limitation of diffusion. Brain-CT showed a partial interventricular hemorrhage and subarachnoid hemorrhage in the left parietal lobe (Figure 2a-d). During the abdomen Ultrasound imaging, a thin septate cyst in the right adnexa was found, which was 15 mm in length, incidentally. During the physical examination, hyperextensibility, obvious forehead, small chin, and enlarged (15 mm) inter-alar width (Figure 3a) were noticed. The left foot was six-fingered (Figure 3b). However, asymmetric face, rough skin, and high or cleft palate were not observed. A homozygous variant (c.2071G>A; p. Val691Met) of *DOCK8* (NM_001190458) was detected in the patient using a clinical exome sequencing kit (Sophia™, Saint Sulpice, Switzerland) on a next-generation sequencing platform (NextSeq 500® System, Illumina, USA). This is the variant AR form of JS. Due to suspicion of Shaken baby syndrome, social investigation was conducted by social service. Subsequently, custody was taken from her parents. Currently, the patient was discharged. She is still followed by ophthalmologists at proper intervals with in terms of ROP. It was determined that our patient's disease may have caused these allegations, involving physical abuse.

The social investigation report revealed that the parents of our case were poor people, but they were interested in their children. According to the information taken from their neighbors and impression from the behaviors of the parents of our case do not give rise to any doubt of harm to their children. The parents were found to have enough ability to raise their children by the social workers who prepared the report.

Informed voluntary consent form: The consent form was taken from the parents of the patient.

Discussion

All physicians, especially pediatrists, forensic medicine, and emergency medicine specialists, can address child maltreatment at any time. At that moment, it is important that making a true diagnosis and declaring it to the legal authorities will prevent further traumas and even death. On the other hand, making an incorrect diagnosis of abuse may cause great injustice for the caregiver or parents of the child. At this point, the diagnosis of the physician is critical. Some cases, as well as ours, may manifest unusual findings that make the correct diagnosis harder. In these cases, a multidisciplinary approach is vital. A JS case very rarely seen was shared with the aim of drawing attention to colleagues on this topic. The purpose of our presentation was to remind and underline the skeletal findings of JS. It has been stated that JS can be due to

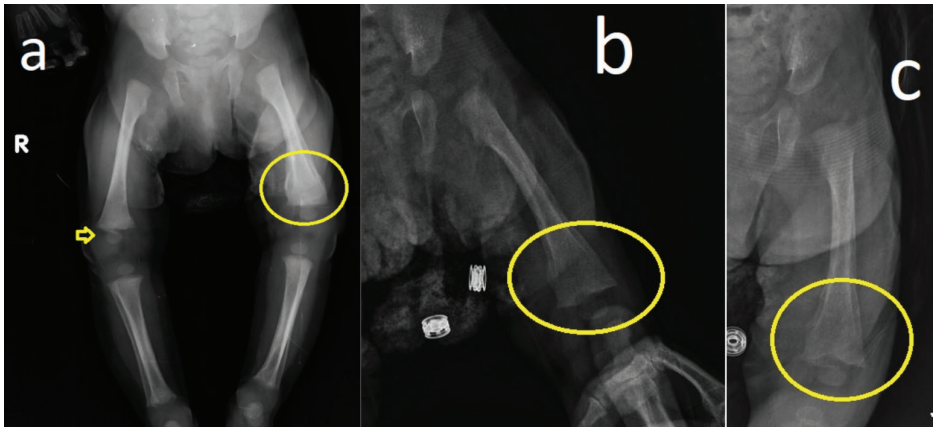

Figure 1. a) Fracture line in the right femur and callus tissue in left femur, **b, c)** callus tissue in left femur

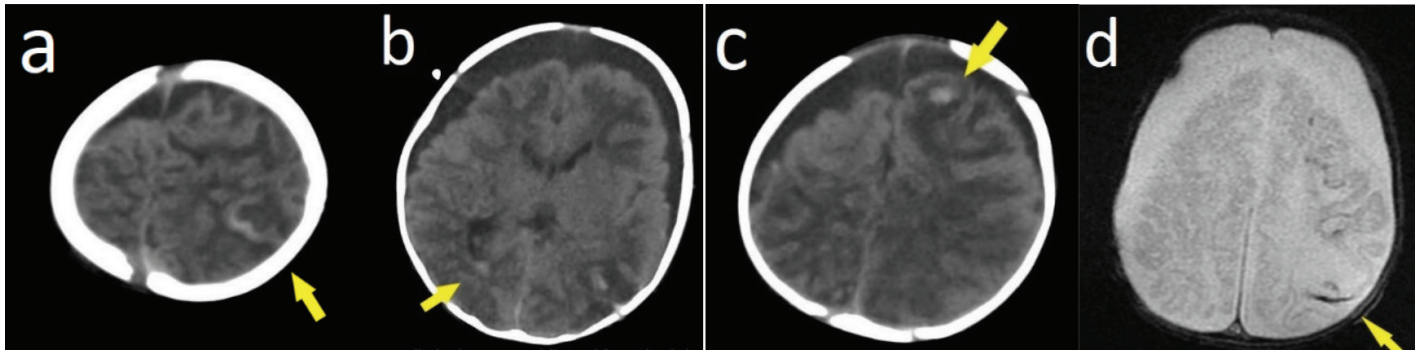

Figure 2. a) Subarachnoid hemorrhage in the left parietal lobe, **b)** interventricular hemorrhage and subdural effusion, **c)** parenchymal hematoma in the left frontal lobe, **d)** subarachnoid hemorrhage in the left parietal lobe

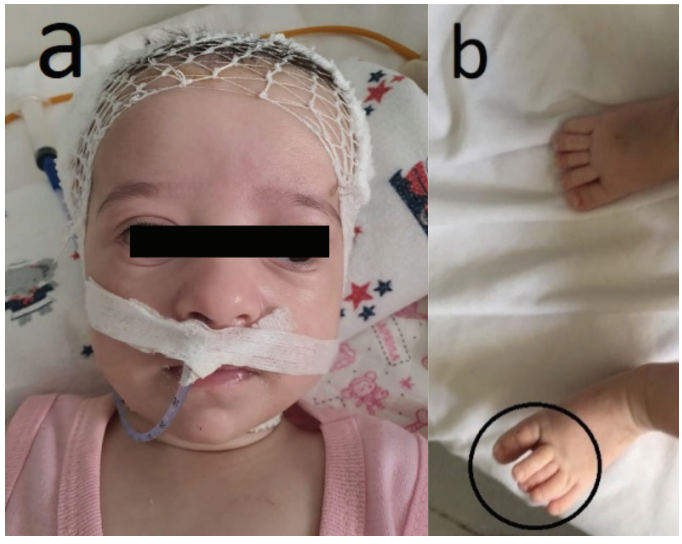

Figure 3. a) Dismorfic findings, **b)** sixt finger in left foot

skeletal and connective tissue abnormalities.[4] Thus, physicians keep findings of those syndromes and diseases in their minds while making a diagnosis of physical abuse.

The etiology of femur shaft fractures in infants is fall accidents, fragility of the bone, and trauma without accident.[5] Femur shaft fracture in infants is very rare.[5] The incidence of femur shaft fracture in children under one year of age is 0.016% per year in Sweden.[5] In a study based on the investigation of the etiology of long bone fractures in infants involving 187 infants, it was reported that two birth-related femur fracture cases were met and they were taken osteogenesis imperfecta diagnosis.[5] In the same study, three cases were rickets.[5] some cases that were suspected of physical abuse were consulted to the register of children and young persons subjected to child welfare measure, but none of them were abused.[5] Femur shaft fractures can be linked with physical abuse in children under one year of age, underlining the significance of differential diagnostic consideration.[5] Von Heideken et al.[5] reported that the proportion of femur fractures in abuse cases was 9% among 287 cases in the study. Abulebda et al.[6] shared a case who was one and half years old and had bilateral femur, humeral, and tibia fractures. The case was drawn attention and searched by child protective services.

Although JS has many subtle features such as dysmorphic face and hyperlaxity of joints, these findings should raise the index of suspicion of JS. JS contains characteristic features such as asymmetric face, increasing inter-alar width, osteopenia, pathological fractures even if exposing a small trauma, hyper extensible joints, and vascular abnormalities. Our case also

had these abnormalities, so it has shown consistency with the literature.[3] Our case not only had interventricular hemorrhage but also subarachnoid hemorrhage.

Our case is the AR form of JS. It is likely benign according to American College of Medical Genetics and Genomics criteria and uncertain in significance according to ClinVar (www.ncbi.nlm.nih.gov/clinvar/). This variant was found to be heterozygous in two different patients previously diagnosed with common variable immunodeficiency in the literature.[7] Although it was only reported in a heterozygous form in GenomAD (genome aggregation database), it was important that it was homozygous in our case.

Conclusion

JS has different components that cause confusion in the physician's mind to make a diagnosis only on the clinical aspect. It is clear that JS is difficult to diagnose without any genetic testing. During the evaluation of a child with trauma findings such as fractures, some diseases such as rickets, osteogenesis imperfecta, and JS should be considered before the diagnosis. Pediatricians, pediatric radiologists, forensic medicine specialists, and emergency physicians must be aware of these probabilities. This case was found to have a mutation, *DOCK8*, suggesting JS. Unfortunately, the levels of serum immunoglobulin E could not be tested because of the busy laboratory conditions of the pandemic. Nevertheless, common infections that our case met, eosinophilia, and decreasing lymphocyte and white blood cell levels may support our diagnosis. The fractures were most likely due to JS. Abandoning the misdiagnosis of abuse cases requires attention and an approach of multidisciplinary medical care.

Information: An abbreviated version of portions of this paper was presented at the 18. Adli Tıp Günleri Congress, Antalya, Türkiye, Oct 19, 2023.

Ethics

Informed Consent: The consent form was taken from the parents of the patient.

Authorship Contributions

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

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References

1. Tıraşçı Y, Durmaz U, Altınal A, Bulut K, Özdemir Y, ve ark. "Dicle Üniversitesi Adli Tıp Anabilim Dalınca 2012-2015 yılları arasında düzenlenen adli raporların retrospektif olarak değerlendirilmesi." Dicle Tıp Dergisi. 2016;43:424-30.
2. Oestreich AE, Care MM. Recognizing child abuse in radiology. Switzerland: Springer;2017.
3. Yong PF, Freeman AF, Engelhardt KR, Holland S, Puck JM, Grimbacher B. An update on the hyper-IgE syndromes. Arthritis Res Ther. 2012;14:228.
4. Christian CW, States LJ. Medical Mimics of Child Abuse. AJR Am J Roentgenol. 2017;208:982-90.
5. Von Heideken J, Thiblin I, Högberg U. The epidemiology of infant shaft fractures of femur or humerus by incidence, birth, accidents, and other causes. BMC Musculoskelet Disord. 2020;21:840.
6. Abulebda K, Abu-Sultaneh S, Lutfi R. It is not always child abuse: multiple fractures due to hypophosphatemic rickets associated with elemental formula use. Clin Case Rep. 2017;5:1348-51.
7. De Valles-Ibáñez G, Esteve-Solé A, Piquer M, et al. Evaluating the Genetics of Common Variable Immunodeficiency: Monogenetic Model and Beyond. Front Immunol. 2018;9:636.