Major Depressive Disorder mimicking Mental Retardation: A rare case of Joubert Syndrome

Mental Retardasyonu taklit eden Major Depresif Bozukluklu nadir bir olgu: Joubert Sendromu

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SUMMARY

Joubert Syndrome is a rare genetic and clinical disorder that affects many different parts of the body, especially the central nervous system, musculoskeletal system, kidneys, eyes, respiratory system, endocrine system and liver. In addition to all these affected organ systems, dysmorphic facial features can also be observed in people with Joubert Syndrome. Symptoms and clinical signs in individuals with Joubert Syndrome vary greatly in several ways, to the extent where afflicted individuals even from the same family might have completely different clinical presentations, when compared to one another. Although the clinical features of Joubert Syndrome appear in the neonatal period, the diagnosis can usually take years after the symptoms appear. A prevalence of between 1 per 80 000 and 1 per 100 000 live births has been reported by many investigators. Despite its heterogenous symptom cluster, poor outcome in cases of Joubert Syndrome presenting predominantly with hypotonia and global developmental delay has been reported. Although mental retardation has been reported as the primarily anticipated psychiatric condition in cases with Joubert Syndrome, some other clinical sources within relevant literature identify autism spectrum disorders as another possible psychiatric diagnosis observed in affected individuals. It is known that there are a limited number of cases with Joubert Syndrome, it is a rare condition and the main psychiatric finding expected in the course of the syndrome is mental retardation. With this case report, we have aimed to discuss a case of Joubert Syndrome who had presented with symptoms of major depressive disorder that mimicked mental retardation.

Keywords: Joubert Syndrome, Major Depressive Disorder, Mental Retardation

ÖZET

Joubert Sendromu özellikle santral sinir sistemi, kas-iskelet sistemi, böbrekler, gözler, solunum sistemi, endokrin sistem ve karaciğer olmak üzere vücudun birçok kısmını etkileyen klinik ve genetik nadir görülen bir hastalıktır. Joubert Sendromu olan kişilerde tüm bu etkilenen organ sistemlerine ek olarak dismorfik yüz özellikleri de gözlenebilmektedir. Aynı ailenin üyeleri olsalar dahi Joubert Sendromu'na sahip kişilerdeki belirtiler ve semptomlar birçok düzeyde farklılık gösterebilir. Joubert sendromuna ait klinik özellikler yenidoğan döneminde ortaya çıkmasına rağmen, tanının konulması genellikle semptomların ortaya çıkışını takiben yıllar sonrasını bulabilmektedir. Joubert Sendromu her 80 bin doğumda bir ile her 100 bin doğumda bir oranları arasında görülebilmektedir. Joubert Sendromu'nun belirti kümesi heterojen olmakla birlikte, hipotoni ve motor mental gerilikle seyreden vakaların prognozu kötüdür. Joubert Sendrom'lu olgularda psikiyatrik belirti olarak mental retardasyon beklense de bazı kaynaklarda bu olgularda otizm spektrum bozukluklarına da rastlandığı belirtilmiştir. Joubert sendromuna sahip sınırlı sayıda olgu bulunduğu, nadir görülen bir sendrom olduğu ve sendromun gidişatında beklenen temel psikiyatrik bulgunun mental retardasyon olduğu bilinmektedir. Bu olgu sunumunda mental retardasyonu taklit eden major depresif bozukluk semptomlarıyla prezente olan Joubert Sendromu olgusunu tartışmayı amaçlamaktayız.

Anahtar Kelimeler: Joubert Sendromu, Majör Depreşif Bozukluk, Mental Retardasyon

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INTRODUCTION

With its estimated prevalence as between 1 per 80 000 and 1 per 100 000 live births, Joubert Syndrome(JS) is a rare genetic disorder with autosomal recessive inheritance, characterized by partial or total absence of cerebellar vermis (1,2). Making a formal diagnosis for the syndrome is challenging, due to phenotypical variance. No specific gene has been identified for the syndrome so far, as well as absence of pathognomonic biochemical findings (2). Mutations in over 30 genes responsible for protein synthesis of cellular structures, also known as primary cilium that have major role in detection of physical medium and chemical signals, might cause Joubert Syndrome (1,3). Clinical and neuroradiological characteristics need to be evaluated together, in order to make a formal diagnosis. Even though clinical features might emerge as early as during the neonatal phase, it generally takes years to make the diagnosis. Common clinical symptoms of the syndrome include ataxia, hypotonia, abnormal eye movements, nystagmus, episodes of hyperpnea-apnea, and global developmental delay (3). Specific facial features such as broad forehead, low-set ears, triangle-shaped mouth, hypertelorism, arched eyebrows, droopy eyelids might alert the clinican to further evaluate the child for a possible JS diagnosis (4). In most affected individuals, developmental delay and mental retardation that varies from moderate to severe forms are common, though in some studies, autism spectrum disorder has also been reported as another psychiatric condition accompanying the course of the syndrome (5,6). Despite its heterogeneous symptom cluster, poor outcome in cases of Joubert Syndrome presenting predominantly with hypotonia and global developmental delay has been reported (7). Distinctive neuroradiological feature of Joubert Syndrome has been identified as the combination of cranial abnormalities caused by problems in the development of rear structures of the brain, including cerebellar vermis and the brainstem, also known as the molar tooth sign that is visible via brain imaging studies, like Magnetic Resonance Imaging (MRI). This specific radiological sign was named after the characteristic brain abnormalities' resemblance to the cross-section of a molar tooth, when seen on an MRI (1,3,7).

Major depressive disorder is an episodic psychiatric disorder that presents with depressed mood, loss of interest, restlessness, decreased energy, impaired cognitive functions, and a combination of vegetative symptoms such as alterations in sleep and appetite (8). Symptoms of the disorder might vary based on the age, gender, education level and cultural characteristics of the child. Prevalence studies of major depressive disorder in school aged children have reported an estimated value of approximately 2%, with no gender dominance for given ages (8). Even though cases with JS were mainly expected to meet the criteria for intellectual disability as the index psychiatric condition, following an in-depth assessment, we have determined that our case had age-appropriate cognitive functioning and symptoms observed were actually reflective of another psychiatric disorder underneath, that was major depressive disorder. With this case report, we aim to discuss a case of Joubert Syndrome who is presented with symptoms of major depressive disorder that mimicks mental retardation. Secondary purpose of this case report is emphasizing the importance of performing an elaborative clinical evaluation and taking a detailed history from the patient and their parents in the psychiatric evaluation and diagnosis process.

CASE

The case was a 7 year 3 months old male who had been brought to child and adolescent psychiatry unit in order to formally apply for a request to renew his disability report given by the health board of the institution. Gathered from the anamnesis obtained by interviewing the mother, it was learned that the case was being followed up by child neurology and child nephrology units due to conditions involving developmental delay starting from birth, disruptions in the EEG, a history of seizures and chronic renal failure. In his last disability report, the case was also diagnosed with mild mental retardation and speech problems. The case had born at 38 weeks with a birthweight of 4750 grams, and had a history of deoxygenation at delivery and difficulties in sucking while being breastfed, later on. When his developmental history was interrogated in detail, it was learned that the case had managed to hold his head up at 2 years old, sit without any support at 3, walk at 4,5, and

speak his initial words at 6 years of age, though he had significant articulation problems as observed during interaction and communication. It was also learned that the case had a history of delayed potty training due to his diagnosis chronic renal failure, and wore diapers at nighttime since he continued to wet his bed asleep. The mother stated that the case had started to understand what the other person said to him from very early on and tried to accomplish the task, but failed to do what had been asked due to his problems in motor coordination, which was also observed by the staff at the time of evaluation. Physical features such as droopy eyelids, wide forehead, different mouth shape, slightly low-set ears, dysmorphic facial structure along with his expression depicting low mood were striking and he refrained from making eye contact until the end of the session. He mainly replied to questions being asked and efforts to form a connection by shrugging. Upon initial examination, the case was referred to be further evaluated by the hospital's medical genetics department due to his sustained history of multiple system pathologies and dysmorphic facial structure. WISC-R test requested to have an assessment of the case's intellectual functioning failed to provide additional information since he was unmotivated, inattentive to the test material, did not have any eye contact at all, refused to speak and was not very well adjusted to the test environment. At this point, we decided to add up some more sessions to the assessment phase. Following sessions with the case and mother revealed that although the case was very eager to maintain communication, his articulation problems caused other individuals finding it hard to understand what he had said and so in time, he started to refuse to speak, became much more socially withdrawn due to him being left out by peers, declined to spend time and play with his peers, was aggressive and engaged in self-harm behavior when unable to express himself, was embarrassed to have his mother aid him to meet his daily needs such as eating with other adults and peers, cleaning after using the restroom (because of his problems regarding limitations in motor skills), tended to spend all his day at home in his room, and showed interest in almost nothing. It was noticed that the case had no problems in speaking to his mother, since he knew he would be understood. After forming a therapeutic alliance with the case following many individual sessions, it was observed that the case actually understood what he was being told, started expressing himself with body movements and sign language when unable to do so verbally or verbal limitations occured, and he actually had an ability to understand emotions and express them as well as abstract and concrete thinking, identical to his peers. Always appearing with his mother in his outpatient sessions, it was learned that the case had very limited relationship with his father and that the father had a neglectful attitude towards his family. In the molecular karyotyping analysis applied following a medical genetics consultation, it was determined that the case had a homozygotic deletion involving 2 genes that binded 35 probes with a magnitude of approximately 102.261 kb on the long arm of the second chromosome. Results of genetic analyses collected from the parents both yielded heterogeneous loss within the same location of the second chromosome. As a result of all assessments, the patient's intellectual level was determined to be higher clinically, compared to what would have been expected of a case with JS, and that he did not meet the criteria for a diagnosis of mental retardation. His symptoms of refusal to speak, becoming much more withdrawn, depressed mood, aggression and irritability, and overall decrease in general interest or pleasure were linked to a diagnosis of major depressive disorder. Symptoms such as depressed mood (feeling sad and empty, appearing unhappy and tearful), irritable mood and agression, markedly diminished interest and pleasure, psychomotor retardation, loss of energy and fatigue observed in our case for at least 2 weeks are compatible with DSM-5 diagnostic criteria for major depressive disorder. Upon the diagnostic process, we have started following up the case for both his psychiatric disorder and family relationship problems. During the 1 year follow-up period, the case has received fluoxetine 20 mg drug treatment and supportive management. As a response to the treatment, the patient's depressive symptoms have been subsided.

DISCUSSION

The case was brought to the child and adolescent psychiatry unit for the treatment of his speech disorder and motor retardation and for the renewal of his disability report which was previously pre-

pared with the diagnosis of mental retardation. The patient's dysmorphic facial appearance, motor retardation, the history of deoxygenation following delivery and difficulties in breast-feeding were consistent with the defined Joubert Syndrome clinic. (7,9). As a result of, regular outpatient follow-up and clinical assessments, it was understood that even though the case had a history of speech delay, his language skills had developed by age and his current speech problem was articulation disorder. Additionally, it was observed that the case actually refused to speak in social outlets since his speech was not understood by other people and his mental capacity was compatible with his peers and developmental level. Among predominant symptoms of depression in children are social withdrawal, avolition and loss of interest (8,10). Symptoms of our case at the time would fit this profile. Since the mental capacity of the case is considered within normal limits, the patient was aware of his speech disorder, motor retardation, that he needed his mother's help to continue his daily functions, and his father's neglectful attitudes. It is thought that all these paved the way for the decrease in self-esteem, social withdrawal and depression in the patient.

Even though; no research has been found in the relevant literature evaluating the possibility of a link between major depressive disorder and JS, we believe it would be important to underline the need to undergo a detailed psychiatric examination for individuals diagnosed with JS. Although many cases of JS are presented with mental retardation as the primary psychiatric condition, our case had normal intellectual functioning, and the delay in his developmental milestones as well as limited functioning, were due to his underlying neurological motor retardation tied to the syndrome.

It is especially hard to diagnose depressive disorder in small children, mainly because of the natural and expected underdevelopment of their verbal skills and emotion regulation etc, as well as the negative impact depressive mood exerts on cognitive functions (9). For all these reasons, major depressive disorder might mimic cognitive delay and intellectual disability in children. Symptoms of our case at the time of application mimicking mental retardation and since intellectual disability was a frequent and anticipated component of JS, clinicians that had evaluated the case before might have diagnosed him with mental retardation. However cases like this one; shows us the importance of carrying out an elaborate clinical assessment and history, obtaining information about the behavior patterns and human relations in the various environments, and making detailed observations in each case that applied to us. We would like to emphasize the importance of regular outpatient follow-ups and evaluation interviews in order to complete these necessary processes in order to make the correct diagnosis in all cases who applied to us (11). It is only possible to create the most appropriate treatment plan once we are able to make the right diagnosis, and provide optimum levels for resuming psychiatric well being of our patients.

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KAYNAKLAR

1.Hardee I, Soldatos A, Davids M, Vilboux T, Toro C, David LK, Ferreira CR, Nehrebecky M, Snow C, Thurm A, Heller T, Macnamara EF, Gunay-Aygun M, Zein WM, Gahl WA, Malicdan MCV. Defective ciliogenesis in INPP5E-related Joubert syndrome. Am J Med Genet A 2017;173:3231-3237. doi: 10.1002/ajmg.a.38376.

2.Travaglini L, Brancati F, Silhavy J, Iannicelli M, Nickerson E, Elkhartouf N, Scott E, Spencer E, Gabriel S, Thomas S, Ben-Zeev B, Bertini E, Boltshauser E, Chaouch M, Cilio MR, de Jong MM, Kayserili H, Ogur G, Poretti A, Signorini S, Uziel G, Zaki MS, Johnson C, Attie´-Bitach M, Gleeson JG, Valente EM. Phenotypic spectrum and prevalence of INPP5E mutations in Joubert syndrome and related disorders. Eur J of Hum Genet 2013;21:1074–1078. doi: 10.1038/ejhg.2012.305

3.Romani M, Micalizzi A, Valente EM. Joubert syndrome: congenital cerebellar ataxia with the molar tooth. Lancet Neurol 2013;12:894-905. doi:10.1016/S1474-4422(13)70136-4.

4.Braddock SR, Henley KM, Maria BL. The face of Joubert syndrome: a study of dysmorphology and anthropometry. Am J Med Genet A 2007;15;143A:3235-3242. doi: 10.1002/ajmg.a.32099.

5.Takahashi TN, Farmer JE, Deidrick KK, Hsu BS, Miles JH, Maria BL. Joubert syndrome is not a cause of classical autism.

Am J Med Genet A 2005;132A:347-351. doi: 10.1002/ajmg.a.30500.

6.Bachman-Gagescu R, Dempsey JC, Phelps IG, O'Roak BJ, Knutzen DM, Rue TC, Ishak GE, Isabella CR, Gorden N, Adkins J, Boyle EA, de Lacy N, O'Day D, Alswaid A, Ramadevi AR, Lingappa L, Lourenço C, Martorell L, Garcia-Cazorla À, Ozyürek H, Haliloğlu G, Tuysuz B, Topçu M, Chance P, Parisi MA, Glass IA, Shendure J, Doherty D. Joubert syndrome: a model for untangling recessive disorders with extreme genetic heterogeneity. J Med Genet 2015;52:514-522. doi: 10.1136/jmedgenet-2015-103087.

7.Poretti A, Snow J, Summers AC, Tekes A, Huisman TAGM, Aygun N, Carson KA, Doherty D, Parisi MA, Toro C, Yildirimli D, Vemulapalli M, Mullikin JC, Cullinane AR, Vilboux T, Gahl WA, Gunay-Aygun M. Joubert Syndrome: Neuroimaging Findings in 110 Patients in Correlation with Cognitive Function and Genetic Cause. J Med Genet 2017;54:521-529. doi: 10.1136/jmedgenet-2016-104425.

8.Birmaher B, Brent DA. Depressive and disruptive mood dysregulation disorders in Dulcan's Textbook of Child and Adolescent Psychiatry Second Edition. Editor Dulcan MK. Arlington, VA, American Psychiatric Association Publishing, 2016, pp. 245-276.

9.Crawford D, Dearmun A. Joubert Syndrome. Nurs Child Young People 2017;29:15-15. doi: 10.7748/ncyp.29.5.15.s19.

10.Mullen S. Major depressive disorder in children and adolescents. Ment Health Clin 2018;8:275-283. doi: 10.9740/mhc.2018.11.275

11.Öztop DB. Okul Çağı Çocuklarında Ruh Sağlığının Değerlendirilmesi in Çocuk ve Ergen Ruh Sağlığı ve Hastalıkları Second Edition. Editors Pekcanlar Akay A, Ercan ES. Ankara, Türkiye Çocuk ve Genç Psikiyatrisi Derneği Publishing:9, 2016, pp. 12-17.