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BAINBRIDGE ROPERS SYNDROME AS A RARE CAUSE OF AUTISM SPECTRUM DISORDER

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INTRODUCTION

Bainbridge-Ropers syndrome (BRPS) was first described in 2013 (Bainbridge et al. 2013). BRPS (Online Mendelian Inheritance in Man (OMIM):615485) is a genetic syndrome resulting from an alteration in the function of the transcriptional regulator Additional Sex Combs Like 3 (ASXL3) gene (https://www.omim.org/entry/615485). ASXL3, the pathogenic gene of the rare BRPS, is a member of the ASXL gene family, located on 18q12.1, 6.8 kb in length, containing 12 exons and encoding polycomb protein (Bainbridge et al. 2013). This gene family is a group of transcription factors that regulate target genes at the chromatin level through epigenetic modification and has been reported to play a role in embryonic development, cell proliferation, and tumorigenesis (Micol et al. 2016). ASXL3 is expressed in various tissues, including the brain, spinal cord, kidney, liver, and bone marrow (Sahtoe et al. 2016). While the full functions of the ASXL3 gene/protein are currently unknown, it is known to play a modulatory role in cells in different organs at various stages of development, making changes in this gene potentially affecting various parts of the body differently. BRPS occurs because of a de novo mutation in the ASXL3 gene in the sperm or ovum before fertilization. In other words, mutations in ASXL3 that cause BRPS are not usually inherited from one parent (Balasubramanian et al. 2017). BRPS is characterized by several features, including low birth weight, nutritional problems, growth retardation, mental retardation, autism, hypotonia, dysmorphic face, and speech delay due to the de novo mutation in ASXL3 (Russel et al. 2012, De Rubeis et al. 2014, Hori et al. 2016, Shashi et al. 2017). Due to its rarity, there are only limited case reports on BRPS, leading to its diagnosis and treatment difficulties.

This case report aims to contribute to the literature by presenting a patient diagnosed with BRPS who received follow-up at our autism spectrum disorder clinic in the outpatient unit. The report discusses the case in the context of current literature findings on BRPS, adding valuable insights to the existing knowledge.

CASE REPORT

Twenty-four-month-old boy was admitted to paediatric neurology with complaints of inability to walk and speak. In his medical evaluation, the weight of the child was determined as 10 kg (3-10 percentile) and height as 82 cm (10-25 percentile). During the examination, the child exhibited dysmorphic features, including scaphocephaly, a prominent forehead, arched eyebrows, downward-oblique palpebral fissures, and a high palate. The examination of the heart and lungs showed normal sounds without any additional sounds or murmurs. The abdomen was slightly distended, but no organomegaly was observed. Male external genitalia were observed. The lower and upper extremities were hypotonic with a 3/5 reduced strength. There was a slight increase in deep tendon reflexes. The child's hemogram, biochemistry parameters, thyroid parameters, iron profile, zinc, copper, and lead levels were normal. The urine test for a very long chain fatty acid, organic acids, and mucopolysaccharidoses was negative. Scans for tandem MS, biotinides activity, and sphingolipidoses were negative. Electroencephalography, ectomy and hearing tests evaluated in the investigation of hypotonicity were within normal limits. The child psychiatry outpatient clinic was consulted because of the examinations and examinations performed by the paediatric neurologist. During the medical history obtained from the mother, it was noted that the child has not achieved walking and has limited speech, mainly making simple sounds. The child's overall development has consistently behind that of peers. The child was born as the second surviving baby during the second pregnancy, with a normal spontaneous vaginal delivery

and a birth weight of 2750 grams. There were no postnatal incubator care or jaundice issues. The child received breast milk for approximately four months but faced difficulties with sucking, leading to the need to discontinue breastfeeding. It was learned that he started sitting with support at the age of 12 months and sitting without support at the age of 18 months. It was learned that there was no distinctive feature in the family history and that there was no consanguinity between the parents. During the psychiatric examination in the playroom, the toddler, dressed in clothes that made him appear younger than his age, displayed behaviours consistent with his chronological and socio-cultural status. Notably, he was unable to walk independently, did not respond when called, and avoided making eye contact. Furthermore, he exhibited no engagement in the play activities or interest in toys. Throughout the interview, he remained non-verbal, not making any sounds. During the Denver Developmental Screening Test, the child's behaviour was assessed. It was observed that he did not make eye contact with the interviewer and did not respond to the given commands. The results of the test indicated developmental delays in different areas: he demonstrated skills at the level expected for a 14-month-old in the personal-social domain, at the level of a 13-month-old in fine motor skills, at the level of a 9-month-old in language development, and at the level of a 10-month-old in gross motor skills. The Childhood Autism Rating Scale (CARS) score applied by the interviewer was 52. Brain Magnetic Resonance Imaging (MRI) revealed a delay in myelination relative to the patient's age. The child was diagnosed with autism spectrum disorder and motor and mental retardation. Further examination was conducted through genetic testing. The genetic testing included negative results for whole exome sequence (WES), karyotype analysis, and comparative genomic hybridization. Additionally, fluorescent in situ hybridization (FISH) was performed to specifically check for Prader-Willi syndrome.

The initial molecular studies yielded negative results. However, after conducting whole genome sequencing (WGS), a de novo mutation in the ASXL3 gene (NM_030632.3) c.4678C>T(p.Arg1560Ter) was identified. This discovery confirmed the diagnosis of Bainbridge-Robers syndrome. Brain MRI revealed a delay in myelination for the patient's age, while all other imaging studies, including skeletal examination and renal ultrasound, showed normal results. In response to the diagnosis, the patient started receiving special education support to address both mental and physical aspects. Additionally, occupational therapy sessions were initiated, and regular check-ups continue to monitor the patient's progress. It has been determined that the patient's skills, including standing, making eye contact, and following commands, have improved. Before conducting the study, informed consent was obtained from the patient's family, ensuring ethical practice in the medical investigation.

DISCUSSION

Currently, around 30 cases of Bainbridge-Robers syndrome have been documented in the medical literature. However, it is estimated that there are approximately 200 affected children and adolescents worldwide (Verhoven et al. 2018). BPRS is a rare genetic disorder characterized by a dysmorphic face, feeding difficulties, psychomotor retardation, and language-speech disorders. In the prenatal and natal histories of children with BPRS, it has been observed that they are typically born at term through normal vaginal delivery. However, in some cases, caesarean sections were performed due to breech presentation. Additionally, most reported cases of BPRS exhibited intrauterine growth delay and low birth weight. (Balasubramanian et al. 2017). Qiao et al. (2019) reported that the patient was born on time and had low birth weight in a case of twenty-six days.

According to the report by Yang et al. (2020), a six-month-old case with motor and mental retardation was born with low birth weight. Our case aligns with the findings in the literature, as the patient was born at term through normal vaginal delivery and had a low birth weight.

BRPS typically exhibit dysmorphic facial features, which may include downward-sloping palpebral fissures on the outer margins, hypertelorism, arched-to-curved eyebrows, and a prominent forehead. (https://www.omim.org/entry/615485,) A high-arched palate is frequently observed, and a few children may have micrognathia in BRPS. In this case, the patient exhibited scaphocephaly characterized by a long and narrow head shape, along with a prominent forehead, arched eyebrows, downward-sloping palpebral fissures, and a high-arched palate. These findings are consistent with the literature on BRPS (Balasubramanian et al. 2017, Kuechler et al. 2017, Zhang et al. 2018, Cuddapah et al. 2021, Dinwiddie et al. 2013).

In the case report published by Wu et al. (2021), a 42-month-old boy with BRPS was described. The case exhibited trigonocephaly, as well as microcephaly. Furthermore, the patient showed growth and developmental delay, hypotonicity, and delayed speech. These aspects of the case overlap with the findings described in the existing literature on BRPS. Additionally, the reported case received a CARS score of 45, indicating severe autism symptoms and supporting the diagnosis of autism

spectrum disorder. Hori et al. (2016) reported on a five-year-old girl with BRPS and an autism spectrum disorder. The girl exhibited moderate autism symptoms, as indicated by a CARS score of 35.5. This finding suggests that the level of autism symptoms, based on the CARS score, in the case we presented is consistent with the findings in the existing literature. In a study conducted by Balasubramanian et al. (2017) that included twelve cases, it was observed that all children diagnosed with BRPS exhibited moderate to severe motor and mental retardation. Additionally, nine of these children were found to have autism spectrum disorder. In a study conducted by Ikekwere et al. (2021), they examined a total of seven cases diagnosed with BRPS between 2013 and 2020. Among these cases, there were five boys and two girls with an average age of 12. The study reported that 86% of the cases showed delayed cognitive development, 43% exhibited features of autism spectrum disorder, and 29% presented with language-speech disorders. The discrepancy in mean age between this study and the case presented could potentially account for the lack of observed language-speech disorders and autism spectrum disorders in the majority of these seven cases. In the six cases diagnosed with BRPS, as described by Kuechler et al. (2017), five of them exhibited characteristics such as motor and mental developmental delays, limited eye contact, feeding difficulties, hypotonia, a prominent forehead, and challenges with speech and language skills. Our presented case demonstrated similarities to the literature, including comparable birth history, early-life feeding difficulties, dysmorphic facial features, and hypotonia. Additionally, this case also displayed psychiatric symptoms such as motor and mental retardation, language-speech disorders, and an autism spectrum disorder (Zhang et al. 2018).

Opitz syndrome (BOS), caused by an ASXL1 gene mutation, shares overlapping symptoms with the presented case, including developmental delay, hypotonia, and feeding difficulties, which warrant consideration in the differential diagnosis. However, distinguishing features of BOS encompasses a distinct facial appearance with nevus flammeus and exophthalmos on the forehead, unlike the dysmorphic facial symptoms observed in our case. Furthermore, the absence of a flexion posture, which is characteristic of BOS, sets it apart from the presentation observed in our case (Cuddapah et al. 2021, Russell et al. 2018). Shashi-Pena Syndrome, caused by an ASXL-2 gene mutation, is another ASXL-related syndrome that merits consideration in the differential diagnosis. While it shares similarities with BRPS, such as developmental delay, hypotonia, and feeding difficulties, it proves helpful in distinguishing itself from BRPS due to the presence of distinct dysmorphic symptoms like nevus flammeus, exophthalmos, and macrocephaly on the forehead (Cuddapah et al. 2021, Shashi et al. 2017). Furthermore, it is worth noting that Shashi-Pena Syndrome may also exhibit hypoglycaemia and ketoacidosis as clinical features, along with cerebral atrophy observed on brain MRI. These additional findings help to differentiate our presented case from Shashi-Pena Syndrome (22).

The treatment of BRPS remains largely symptomatic, as there is currently no specific cure for the condition. Managing the symptoms is crucial, and it necessitates seeking paediatric consultation and implementing appropriate interventions for nutritional difficulties and growth-development retardation commonly associated with BRPS. Additionally, it is essential to involve paediatric neurology and physical medicine-rehabilitation departments for a thorough investigation and treatment of the hypotonicity observed in affected children. The symptomatic treatment for BRPS includes applied behaviour analysis, DIR floortime, and early Denver method interventions to address the social-communicative symptoms of autism spectrum disorder. Speech and language therapies target language-speech disorders, while physiotherapy addresses motor retardation. Sensory ergotherapy is used for sensory problems, and special education supports cognitive development delay intervention, considering the child's mental capacity. The basis of BRPS symptomatic treatment involves providing appropriate inclusive education or special subclass education. Although these recommended treatments are symptomatic treatments for the symptoms of the syndrome, the effectiveness of these treatments is not yet known. It is necessary to investigate the long-term efficacy of the treatments applied and specific treatments for BRPS.

Studies have reported that malocclusion affects the quality of life of patients (Gal et al. 2022). In the clinical examination of the patient, it was observed that the palate was higher than normal. Patients with a high palate may exhibit various malocclusions and skeletal dental anomalies (Burchang et al. 1994, Annapurna et al. 2019). Timely treatment is crucial for addressing dental and skeletal anomalies in patients. However, it is worth noting that studies have indicated that the presence of a deep palate may not always be a definitive indicator of malocclusion (Saadeh et al. 2022). For this reason, it is essential to conduct regular and comprehensive dental examinations for patients with BRPS.

CONCLUSION

As a result, although it is rare, it is important to consider BRPS in children with a history of low birth weight, nutritional problems, growth retardation, hypotonia, dysmorphic face and speech delay in examination, who have a history of autism spectrum disorder and delayed cognitive development. For this reason, genetic counselling is essential. After diagnosing the disease, the patient should be referred to a dentist, paediatrician, paediatric gastroenterologist, and paediatric neurologist for evaluating accompanying medical conditions. Child and adolescent psychiatrists play a crucial role in raising awareness, diagnosing BRPS, facilitating appropriate care, and identifying comorbid psychiatric conditions in individuals with BRPS. They also need to assess and address their special needs for educational treatments during follow-up.

Ethical Considerations: Does this study include human subjects? YES

Conflict of interest: No conflict of interest

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