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Case Report

Infantile Macrocephaly and Autism Spectrum Disorder Diagnosed with PTEN Hamartoma Tumor Syndrome: A Case Report

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Abstract

Introduction: Loss of function of the PTEN tumor suppressor gene, due to heterozygous mutation, gives rise to a wide variety of disorders, including macrocephaly/autism syndrome, PTEN hamartoma tumor syndrome, and Cowden syndrome, characterized by high risk of developing thyroid and breast cancer at young age.

Case Report: A 2-years-old male infant with simple macrocephaly was referred to the Developmental clinic due to global developmental delay, with special impairment in speech. On physical examination, he had peculiar facies, with mild and nonspecific dysmorphia, and macrocrania with dolichocephaly. There were no stigmata of neurocutaneous disease. At the age of 5 years and 6 months, the heterozygous de novo variant c.302T > C (p- lle101Thr) in PTEN gene was identified, classified as probably pathogenic. Meanwhile, the patient was diagnosed with autism spectrum disorder with moderate developmental delay.

Discussion: The morbidity and mortality of this syndrome is associated with a higher incidence of cancers, most of them curable if early detected. The correct diagnosis, allowing the establishment of an adequate surveillance program, is therefore essential.

Keywords: Autism Spectrum Disorder; Global Development Delay; Macrocephaly; PTEN Hamartoma Tumor Syndrome; PTEN Macrocephaly/Autism Syndrome; PTEN Gene

Abbreviations

SD: Standard Deviations; ASD: Autism Spectrum Disorder; PTHS: PTEN Hamartoma Tumor Syndrome; CS: Cowden Syndrome; BRRS: Bannayan-Riley-Ruvalcaba Syndrome; PS: Proteus Syndrome; PLS: Proteus-Like Syndrome

Introduction

PTEN is a tumor suppressor gene located on chromosomal region 10q23.3. Loss-of-function mutations of PTEN lead to upregulation of the PI3K/AKT signaling pathway, affecting multiple cellular processes. PTEN has an essential role in neurodevelopment and normal social behavior, where tight control of the PI3K/AKT/mTOR

pathway is of great importance. Macrocephaly is defined as an occipital-frontal circumference more than 2 standard deviations (SD) above the mean for height, sex, and ethnicity. A link between PTEN variants and children with macrocephaly, ranging from + 3SD to + 4SD, with autism spectrum disorder, and with intellectual disability or neurodevelopmental delay, has been demonstrated in several studies [1,2]. A huge variety of phenotypes result from PTEN germline mutations: macrocephaly/autism syndrome, primarily seen in infants, and PTEN hamartoma tumor syndrome (PTHS). PHTS includes Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome (BRRS), PTEN-related Proteus syndrome (PS) and PTEN-related Proteus-like syndrome (PLS) [3].

PTEN-related macrocephaly/autism syndrome, an autosomal dominant disorder, is characterized by abnormal facial features, macrocephaly, and delayed psychomotor development, which in turn results in mental retardation and autistic behavior [4].

CS is a multiple hamartoma syndrome that presents a high risk of benign and malignant thyroid, breast and endometrial tumors in young adults and adults. Arteriovenous malformations, multiple lipomas and other soft tissue tumors may also appear. In their late 20s, affected individuals present with macrocephaly, papillomatous papules, and trichilemmomas. BRRS is a congenital disorder that, in addition to macrocephaly, is characterized by lipomas and pigmented macules of the penile glans and hamartomatous intestinal polyposis. On the other hand, PS is a disorder characterized by limb asymmetry, with excessive growth of hands and/or feet, cranial hyperostosis, vascular and lymphatic malformations and connective tissue and epidermal nevi. PLS is a disorder that, although closely related to the previous ones, individuals present with macrocephaly, lipomas and overgrowth that do not meet the criteria for CS, BRRS or PS [3]. For patients with PHTS, guideline 2020.1 National Comprehensive Cancer Network® (NCCN) recommends that tumor follow-up involves physical examination every year and thyroid ultrasound starting at age 7 years. It also recommends colonoscopy every 5 years from age 35 or earlier, depending on family history of colon cancer, and renal ultrasound every 1-2 years from age 40.

The authors present a case of a patient with a PTEN germline mutation, ASD and macrocephaly.

Case Presentation

Male infant, born after 37 weeks gestation with 3435 g (+ 1.0SD) in weight, 50 cm (+ 0.72 SD) in height and 35 cm (+ 1.13SD) in head circumference. Paternal family history of face "tumors" and maternal family history of behavioral and learning disorders. Two healthy 11- and 18-year-old brothers and a 21-year-old sister with asthma. At 2 years and 9 months he was referred to the Developmental clinic due to macrocephaly and global developmental delay (GDD), with special impairment in speech. His weight was then 17.2 Kg (+ 1.63SD), height97.2 cm (+ 0.54SD) and head circumference 55.9 cm (+ 4.62SD). On physical examination, he had peculiar facies, with minor facial dysmorphisms, and macrocrania with dolichocephaly. There were no stigmata of neurocutaneous disease. Evaluation with Griffiths Mental Development Scale 2nd version revealed an overall developmental quotient (gDQ) of 79%, lower than the mean for his chronological age. Brain magnetic resonance imaging (MRI) did not reveal any abnormal signal in the brain parenchyma. To elucidate the cause of macrocephaly and progressive worsening of GDD, he was referred to Genetics clinic genetic at the age of 4 years and 11 months, and genetic testing was performed after parent's informed consent. By then, clinical observation revealed deficits in social communication and interaction, lack of eye contact, difficulties with environmental transitions, and problems with behavior adjustment. The Wechsler Preschool and Primary Scale of Intelligence - Revised psychometric test (WPPSI-R) was the instrument to assess cognitive development – his full-scale intelligence quotient (IQ) was 86 (77, verbal IQ, and 101, performance IQ). Based on suggestive findings in Autism Diagnostic Interview-Revised (ADI-R) and Autism Diagnostic Observation Schedule (ADOS), and according to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) criteria, ASD was diagnosed. Genetic testing revealed a heterozygous likely pathogenic variant, c.302T > C (p-lle101Thr), in exon 5 in PTEN gene. Parental genetic counselling and testing was performed, confirming a de novo variant in the proband. The diagnosis of PTEN-associated macrocephaly/ASD was made.

Discussion

Paracetamol Our patient had a heterozygous missense variant of PTEN (c.302T > C) in exon 5, previously described as probably pathogenic [5]. Exon 5 is considered an essential hotspot for the correct functioning of PTEN as it encodes the catalytic domain of N-terminal phosphatase [6]. Patient was born with a head circumference with a SD of + 1.13, and only later macrocephaly was identified. These data corroborate other study that argued that newborns who develop macrocephaly and ASD later had head circumferences within normal limits at birth. Head growth rates began to accele-

rate during the first year of life until age 4 years, and then slowed down again, with a premature stop [7].

Brain MRI can be a useful tool in the investigation of these patients. According to a recent study, the presence of multifocal static white matter abnormalities and the presence of dilated perivascular spaces may suggest, in patients with ASD and/or macrocephaly and neurodevelopmental delay, a PTEN spectrum disorder [8]. However, as in our case, brain MRI may be normal.

After realizing that PTEN was a tumor suppressor gene, several studies were carried out that proved that its absence was directly linked to the appearance of a high number of cancers. Tan et el reported lifetime risk of a wide variety of cancers in individuals with a germline PTEN mutation (thyroid, breast, endometrial, melanoma, colorectal, and renal cell). The earliest reported cancer was melanoma at 3 years of age [5]. In children, pediatricians tend to focus attention on autism, macrocephaly and delayed psychomotor development [9]. Smpokou., *et al.* reported the case of a 7-year-old child with thyroid cancer whose clinical discretion could allow better formulation of clinical guidelines in PHTS cases. It is therefore important to carry out a follow-up assessment of cancer incidence and carry out total and lifelong medical management.

On this basis, we performed ultrasonography of the thyroid gland and found no abnormalities. As for hamartomas of the gastrointestinal tract, we did not perform endoscopic examination because there are no reports of their occurrence in childhood. Since the possibility of cancer is lower for male children than for female children, we examine the breasts only by inspection and palpation [10]. In our case, there were no café-au-lait spots on the skin or lipomas.

Conclusion

PTEN testing should always be taken into account in cases of ASD and/or cases of association of neurodevelopmental delay with macrocephaly. Genetic counseling is needed to alleviate the psychosocial anxiety of PHTS patients and their parents regarding cancer predisposition and developmental problems and to guide multidisciplinary follow-up. Genetic counseling is also helpful for other family members who may also be at risk. Overall, multidisciplinary long-term follow-up is essential for soft-tissue tumors, thyroid cancer, breast cancer and gastrointestinal tract hamartomas, as well as psychosocial problems associated with PTHS.

Conflict of Interest

The authors have no conflicts of interest to declare.

This work has not received any contribution, grant or scholarship.

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