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CASE REPORT

Autism spectrum disorder and PTEN hamartoma tumor syndrome – Child and adolescent psychiatric perspective

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Abstract

Introduction: Autism spectrum disorder is a neurodevelopmental disorder characterized by impairments in social communication and social interaction and the presence of restricted, repetitive patterns of behavior, interests, or activities that negatively impact social, occupational, or other domains. Certain clinical features in autism spectrum disorder patients could raise suspicions of a syndromic form, such as *PTEN* hamartoma tumor syndrome, which is also associated with cancer predisposition in adulthood, in child and adolescent psychiatric appointments. **Case report:** Three pediatric patients with autism spectrum disorder presented clinical features in their physical examination that elicited a suspicion of *PTEN* hamartoma tumor syndrome. Their autism spectrum disorder profile was indistinguishable from idiopathic autism spectrum disorder and did not contribute to clinical pre-test suspicions of *PTEN* hamartoma tumor syndrome. **Discussion:** *PTEN* hamartoma tumor syndrome features should be screened in autism spectrum disorder patients to provide further medical care, including appropriate cancer screening.

Keywords: Autism spectrum disorder. Macrocephaly. *PTEN* hamartoma tumor syndrome.

Perturbação do espetro do autismo e síndrome tumores hamartosos associados ao PTEN – Perspetiva da pedopsiquiatria

Resumo

Introdução: A perturbação do espectro do autismo é uma perturbação do neurodesenvolvimento caracterizada por comunicação e interação social precária e padrões repetitivos de comportamento, interesses ou atividades com impacto negativo nos domínios social, ocupacional e outros. Determinadas características clínicas em pacientes com perturbação do espetro do autismo devem fazer, o pedopsiquiatra, suspeitar de uma forma sindrómica, como a síndrome de tumores hamartosos associados ao *PTEN*, também associada a predisposição para cancro na idade adulta. **Relato de caso:** Três casos pediátricos de perturbação do espetro do autismo com características clínicas ao exame físico que levantaram à suspeita de síndrome de tumores hamartosos associados ao *PTEN*. Operfil de perturbação do espetro do autism foi indistinto dos casos idiopáticos, não permitindo suspeita dirigida d síndrome de tumores hamartosos associados ao *PTEN*. **Discussão:** A síndrome de tumores hamartosos associados a *PTEN* deve ser considerada em determinados pacientes com perturbação do espetro do autismo para que estes usufruam a cuidados médicos personalizados, incluindo o rastreio oncológico.

Palavras-chave: Perturbação espero autismo. Macrocefalia. PTEN

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Keypoints

What is known

- Heterozygous deleterious variants in *PTEN* cause *PTEN* hamartoma tumor syndrome (PHTS).
- The exact prevalence of PHTS in patients with autism spectrum disorder is uncertain, with expected prevalence rates ranging from 1 to 7%.
- An occipital frontal circumference > 3 SD should elicit the suspicion of a PHTS diagnosis in patients with ASD.

What is added

- Despite the variability of the neurodevelopmental profile of PHTS-ASD, it is not currently possible to distinguish it from idiopathic ASD at a child and adolescent psychiatry observation.
- A diagnosis of PHTS-ASD adds to parents' anxiety and fear of the risk of additional health problems, mainly cancer predisposition.
- In cases where a PHTS diagnosis has a negative impact on patients, referral to a child and adolescent psychiatrist should be considered.

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by impairments in social communication and social interaction and the presence of restricted, repetitive patterns of behavior, interests, or activities that negatively impact social, occupational, or other domains[1-3]. It typically occurs early in life, often before the age of three, and is four to five times more common in boys than in girls. It is a complex developmental and behavioral disorder for which prevalence has tripled since 1970[2,3]. The etiology of ASD remains elusive; however, investigations in recent years have hypothesized that environmental and genetic factors contribute to ASD[4-9]. In 0.22-10.02% of ASD cases, a monogenic or copy number variant is identified as a major contributor to ASD, and *PTEN* is an example of a major contributor[10,11].

Deleterious germline *PTEN* variants cause *PTEN* hamartoma tumor syndrome (PHTS), which is characterized by neurodevelopmental disorders, multiple hamartomas, benign skin lesions, and increased susceptibility to cancer, such as breast, thyroid, renal cell, endometrium, and colon cancer, as well as melanoma[1-4]. Neurodevelopmental disorders and macrocephaly are early manifestations of PHTS. Benign skin or oral lesions are common and usually appear in early adulthood. The most common types of benign skin lesions seen are lipomas, acral keratosis, papillomatous skin papules, mucosal papillomas, trichilemmomas, and fibromas[3,4]. The neurodevelopmental profile of individuals with PHTS has a wide range of cognitive features including executive function impairments, elevated rates of intellectual disability, and a high prevalence of ASD[1].

A link between *PTEN* variants, macrocephaly, ASD, intellectual disability, and neurodevelopmental delay, has been demonstrated in several studies. Previous studies have also indicated that a detailed profile of ASD-related behaviors may differ between different genetic syndrome groups and from that seen in idiopathic ASD[12-14].

Since child and adolescent psychiatrists monitor multiple children with ASD, a better knowledge of the clinical features of PHTS-ASD could facilitate the identification of red flags that could elicit further testing.

Materials and methods

From a cohort of 13 patients diagnosed with PHTS and monitored at our center, three pediatric-age cases with ASD were selected.

PubMed research was carried out on June 6-8 using the MeSH terms *"macrocephaly", "autism spectrum disorder"*, and *"PTEN"*. The exclusion criteria were as follows: publication date of more than five years ago. The OMIM platform was consulted and the project was approved by the local ethics committee (017-DEFI/017-CE).

Case reports

Case 1

A male infant born at 34 weeks gestation, with a weight of 2350 g (percentile [P] 57, +0.16 standard deviation [SD]), a height of 46.5 cm (P70, +0.51 SD), and a head circumference (HC) of 36.3 cm (P89, +1.25 SD) to healthy non-consanguineous parents with a healthy younger sibling. At the age of four, the parents brought him for his first medical genetics appointment with concerns about his gait and language regression, which occurred at twelve months of age, and an increased HC. They also reported axial hypotonia since the first month of life and developmental delays in achieving milestones, such as cephalic control at seven months, sentences at five to six years of ages, and diurnal sphincter control at seven years of age. His first words were uttered at thirteen months, but he later regressed.

Upon physical examination, he was found to be macrosomic with a weight and height above P95 and a HC of more than 6.4 SD above the mean. He also presented

with facial dysmorphisms, including frontal bossing, a high forehead, downward-slanted palpebral fissures, a high-arched palate, short neck, 2-3 syndactyly in the hand, frontal angioma, and two lipomas (suprascapular and inguinal regions). Multiple trichilemmomas and arteriovenous malformations were also noted in the leg and glabellar region.

His behavior was disorganized, with increased sensory demand that conditioned his short attention span and task permanence. He required adult supervision to perform tasks and had expressive language impairment, only pronouncing simple vocalizations or isolated words. He displayed limited reciprocal social interaction, except for activities of interest to him, such as sensorimotor activities. His interests were restricted to letters and numbers, and he had a low frustration tolerance. He had received support from speech, occupational, and psychological interventions since age three.

At the age of 53 months, the Ruth Griffiths Mental Developmental Scale showed a psychometric profile below the expected level for his age, with lower results in the locomotor, personal/social, practical reasoning, and eye-motor coordination sub-scales. He was diagnosed with ASD on the basis of suggestive findings in the autism diagnostic observation-scale (ADOS) and Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) criteria. He also fulfilled the criteria for attention deficit hyperactivity disorder (ADHD) and was treated with methylphenidate (MPH), with good tolerance and therapeutic response.

The diagnosis of PHTS was confirmed through the identification of a *de novo* heterozygous pathogenic nonsense variant, c.388C > T (p.Arg130*) in *PTEN*. At his last appointment at nine years of age, his behavior had improved and he was more autonomous in daily activities. He still did not have nocturnal sphincter control, and there was evidence of precarious fine motor skills. Although he was able to read, his understanding and prosody were poor. His working memory and attention levels had improved with MPH. However, he still had deficits in social communication and interaction, difficulties with environmental transitions, and problems with behavior adjustment.

Case 2

A female patient, born at 39 weeks with a birth weight of 3600 g (P76, +0.71 SD), a height of 49 cm (P42, –0.2 SD), and a HC of 37.5 cm (p > 99, +2.95 SD) showed increased HC in the third trimester of gestation. There was no relevant family history of note. Developmental delays were observed, including the ability to sit at nine months, and her first words were uttered at three years of age.

At her first appointment at five years of age, the patient presented with macrocephaly and lipomas on her torso and limbs. During observation, she spent most of the time lying down, visually inspecting her hands while moving them in a stereotyped way and refraining from eye contact. It was challenging to capture her attention even for short periods, and she did not explore toys, except for a game with sounds and lights. She reacted with frustration when interrupted, vocalizing and crying. The patient displayed sensory issues such as displeasure with touch and soap bubbles and appreciated vestibular stimulation.

The Vineland Adaptive Behavior Scales (VABS) indicated a level of adaptive behavior lower than expected for her age. She had a limited range of vocabulary, communicating mostly through gestures and vocalizations of like or dislike. The patient showed considerable difficulty in understanding language and did not have any relationships with peers or adults. She struggled with handling toys and pencils in terms of manual dexterity, balance, hand-eye coordination, and graphomotricity.

A multigene panel for neurodevelopmental disorders was performed to elucidate the etiology of the developmental delay, which revealed a *de novo* heterozygous frameshift pathogenic variant in *PTEN*, c.264del, p. (Pro89Leufs*10), diagnosing this patient with PHTS.

During the last observation at seven years of age, the patient presented high levels of psychomotor agitation and significant motor stereotypes, which made clinical assessment difficult. She was in the first year of school at a special educational unit, where it became evident that her attention parameters were impaired, resulting in poor academic performance. Therapy with MPH was proposed but was refused by her parents. The patient was beginning to show auto- and hetero-aggressive behavior in a context of frustration and difficulties in task or routine transitions.

Case 3

We observed a male born at 39 weeks with macrosomia, weighing 4213 g (P96 +1.72 SD), and measuring 55 cm (P99 +2.6 SD) in length and 39 cm (p > 99, +3 SD) in head circumference (HC). There was no relevant family history. The patient had normal psychomotor development until the age of two, after which he experienced developmental regression. Upon examination, the patient exhibited facial dysmorphic features, including a broad forehead, frontal bossing, macrocephaly, and a depressed nasal bridge. He demonstrated poorly modulated eye

contact, limited communicative intentionality, and a preference for sensorimotor play. The patient's daily routine was hampered by increased vestibular, proprioceptive, and tactile demand, as well as oral hypersensitivity. He vocalized only minimally and showed limited communication abilities.

Genetic testing was conducted to determine the cause of macrocephaly and developmental regression, which revealed a heterozygous, likely pathogenic, missense variant in PTEN, c.139A > G (p.Arg47Gly), confirming the PHTS diagnosis. The patient benefited from therapeutic interventions, including speech therapy, occupational therapy with sensory integration, and psychology. However, he did not cooperate with the development/cognitive standardized assessments.

In his last appointment at six years of age, he presented with impairments in all life contexts, with a clinical diagnosis of ASD with intellectual disability according to the DSM-5 criteria.

Discussion

ASD is a highly heterogeneous disorder with environmental and genetic factors contributing to its etiology[12,13]. The exact prevalence of PHTS in patients with ASD is uncertain, with expected prevalence rates ranging from 1 to 7%[14,15]. Even though the same *PTEN* deleterious variants in different individuals lead to different phenotypes, missense mutations were predominantly reported in PHTS-ASD[16,17]. In our cohort, the type of variants found were heterogenous with one missense, one nonsense, and one frameshift deleterious *PTEN* variant.

The literature stated that individuals with PHTS show a broad neurodevelopmental phenotype with reduced performance in measurements of attention, impulsivity, working memory, reaction time, processing speed, motor coordination, visual-spatial abilities, auditory immediate memory, adaptive function, and more severe intellectual disability compared to idiopathic ASD. It should be noted, however, that reported cognitive abilities varied greatly, with some papers reporting individuals with IQs of over two SD above the population mean (IQ range of 80-135)[1]. In our cohort, all three patients presented intellectual disability. It has been postulated that defects in processing speed and working memory associated with PHTS may be related to poorly-developed white matter[6,8]. People with PHTS and ASD showed frontal deficits in the moderate to severe range accompanied by moderate to severe impairments in intellectual functioning and moderate deficits in both expressive and receptive language suggesting the involvement of a wider region of the brain[6,8]. The literature also suggests that PHTS-ASD patients show deficits in sensory functioning, with the most notable issues on the under-responsive/seeks sensation, low energy/weak, and taste/smell sensitivity subscales of the Short Sensory Profile[18]. Three patients demonstrate a sensory search profile.

The literature reported emotional difficulties only sporadically, but the prevalence of these difficulties may be higher. Hansen-Kiss et al. identified these issues in 34% of their participants, citing anxiety, bipolar disorder, and obsessive-compulsive disorder. "Disruptive" or "problematic" behavior was also reported; however, the precise relationship between different *PTEN* variants and psychological corollaries is yet to be delineated. Evidence showed that those with PHTS-ASD have more difficulties than those with ASD and macrocephaly of different etiology, suggesting that the combination of *PTEN* deleterious variants and ASD may be particularly associated with lower abilities[19-22]. Taken together, this suggests that children with PHTS-ASD might have a distinct neurobehavioral phenotype in multiple aspects of their clinical presentation from patients with idiopathic ASD. These manifestations strongly suggest the importance of reliable genotype-phenotype studies to help with patient management, prognosis, and therapeutic selection by identifying key genetic variants associated with ASD phenotypes[23]. However, this variability of the neurodevelopmental profile associated with PHTS-ASD does not allow child and adolescent psychiatrists to distinguish from idiopathic ASD during clinical behavioral observation. In our PHTS-ASD cohort, the neurodevelopmental profile was indistinguishable from idiopathic ASD.

The macrocephaly associated with ASD is an important "red flag" for diagnosis. Careful physical examination and clinical scoring could increase the clinical suspicion of PHTS, with genetic testing confirming the diagnosis[24]. An occipital frontal circumference > 3 SD should elicit the suspicion of a PHTS diagnosis in patients with ASD or intellectual disability and warn about further features: lipomas, trichilemomas, oral papillomas, arteriovenous malformations, or hemangiomas, with mandatory referral to a physician with experience in this syndrome. This referral would aim to diagnose patients early on and establish an adequate monitoring program given the increased lifetime risk of a wide variety of cancers (thyroid, breast, endometrial, melanoma, colorectal, and renal cell cancer) in patients with PHTS, with specific guidelines for cancer screening[25].

If idiopathic ASD brings with it a requirement for multiple follow-ups, PHTS-ASD adds an anxiety and fear

surrounding the risk of additional health problems, mainly cancer predisposition. Genetic counseling is needed to guide the follow-up and alleviate the psychosocial anxiety of their parents regarding this cancer predisposition. It is also helpful for other family members who may also be at risk of PHTS and would benefit from the knowledge of their reproductive options in positive cases. If the news of the diagnosis has a functional negative impact, referral to a child and adolescent psychiatrist is mandatory.

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Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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