ISSN Print: 2664-8350
ISSN Online: 2664-8369
Impact Factor: RJIF 6.02
IJPN 2026; 8(1): 19-21
www.pediatricsjournal.net
Received: 10-10-2025
Accepted: 13-11-2025

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Severe macrocephaly and PTEN likely pathogenic variant p.(Ala126gly): A case report

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DOI: https://www.doi.org/10.33545/26648350.2026.v8.i1a.179

Abstract
Macrocephaly is a common pediatric finding, but severe or rapidly progressive head growth (OFC >+3 SD) often serves as a sentinel sign for underlying genetic pathologies, such as PTEN Hamartoma Tumor Syndrome (PHTS).
We report the case of a 3-year-old girl presenting with severe, progressive macrocephaly reaching +5 SD at 9 months of age. Clinical findings included café-au-lait-like spots and enlarged perivascular spaces on brain MRI, while hydrocephalus and metabolic disturbances were excluded. Genetic testing identified a heterozygous likely pathogenic *PTEN* variant: c.377C>G p.(Ala126Gly). This specific neomorphic variant is known to alter lipid phosphatase activity, shifting it toward a 5-phosphatase function and potentially carrying distinct oncogenic implications through increased PI3K/AKT signaling. The patient remains neurodevelopmentally stable under multidisciplinary surveillance.
This case highlights the importance of integrating molecular testing into the diagnostic work-up of severe macrocephaly. Early recognition of PHTS is crucial, as it allows for the immediate implementation of lifelong, structured cancer surveillance (targeting thyroid, breast, and renal malignancies) and facilitates accurate genetic counseling. For pediatricians, awareness of PHTS is essential to ensure timely diagnosis and long-term management strategies that significantly alter the patient's prognosis.

Keywords: Macrocephaly, PTEN hamartoma tumor syndrome, Neomorphic variant, cancer surveillance

Introduction
Macrocephaly, defined as an occipitofrontal circumference (OFC) exceeding two standard deviations (SD) above the mean for age and sex, affects approximately 2−5% of the pediatric population [1]. Causes of increased OFC range from benign familial macrocephaly to serious pathological conditions, including genetic disorders. However, severe macrocephaly (OFC >+3 SD) or a rapidly ascending OFC profile must prompt investigation for underlying pathological causes [1].
Among the genetic etiologies, germline mutations in the *PTEN* (phosphatase and tensin homolog) gene have emerged as particularly relevant in pediatrics. *PTEN*, located on chromosome 10q23, encodes a tumor suppressor protein that antagonizes the PI3K/AKT/mTOR pathway, thereby regulating cell growth, proliferation, and survival. Loss of function results in unrestrained signaling, cellular overgrowth, and increased tumor susceptibility [2].
The clinical spectrum of *PTEN* mutations is collectively referred to as PTEN hamartoma tumor syndrome (PHTS), encompassing Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome, and subsets of Proteus and Proteus-like syndromes [2]. Pediatric manifestations often include pronounced macrocephaly, dermatologic findings, and, in some cases, neurodevelopmental disorders such as autism spectrum disorder. PHTS is associated with markedly increased lifetime risks of breast, thyroid, renal, endometrial, and colorectal cancers, as well as gastrointestinal hamartomatous polyposis, necessitating tailored surveillance strategies [2]. PHTS is inherited as an autosomal dominant disorder with penetrance of close to 99% by 30 years (some manifestation), having a transmission risk of 50% for the biological descendants of patients/carriers of PTEN variants.

Genetic counselling is of major relevance, with special focus on identifying at risk relatives that can benefit from surveillance.

Case report

We describe a 3-year-old girl, born at term to healthy, nonconsanguineous parents after a pregnancy notable for polyhydramnios but otherwise uneventful. At birth, her occipitofrontal circumference (OFC) measured +2 SD, with marked diastasis of the sagittal suture and enlarged anterior and posterior fontanelles. The posterior fontanelle remained large for several months, and diastasis persisted until approximately 6 months of age. Early transfontanellar ultrasound was normal. Serial assessments excluded hydrocephalus and abnormalities of thyroid function or phosphocalcic metabolism. Despite this, OFC increased progressively, reaching +5 SD by 9 months of age (Figure 1). At that time, four café-au-lait-like macules were observed. Brain MRI showed no structural malformations but demonstrated enlarged perivascular spaces (Figure 2).

Genetic testing, available at 12 months, revealed a heterozygous *PTEN* variant, c.377C>G p.(Ala126Gly), later reclassified as likely pathogenic. Her father presented with mild macrocephaly and a family history of thyroid disease, but *PTEN* carrier testing for the familial variant was negative. The child remains clinically stable with normal development under annual thyroid ultrasound and pediatric follow-up.

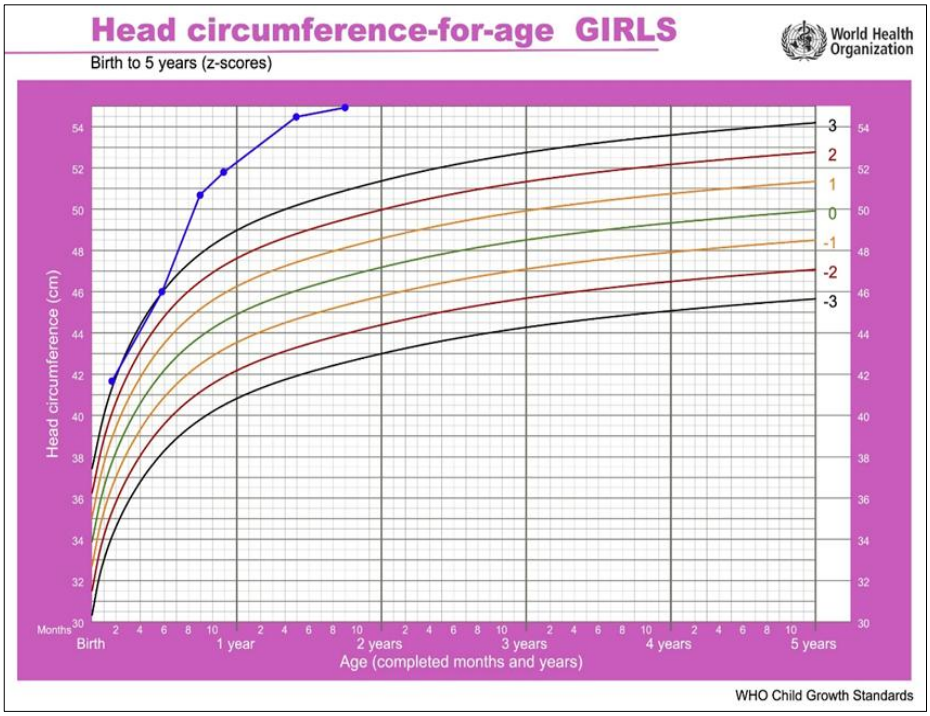

Fig 1: Evolution of patient's Head Circumference according with World Health Organization chart

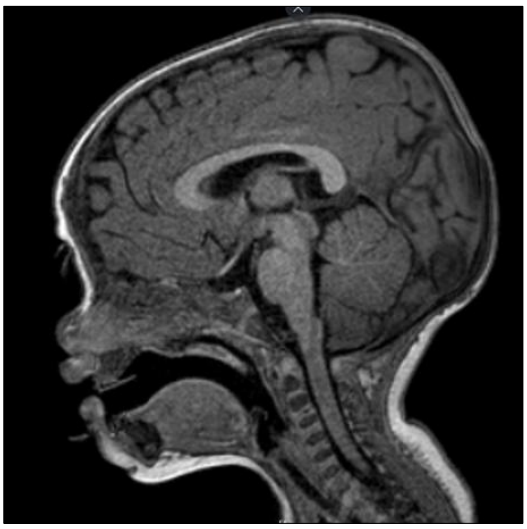

Fig 2: Brain MRI performed at 9 months of age, revealing multiple dilated perivascular spaces in the bilateral parietal subcortical white matter

Discussion

This report illustrates the diagnostic and clinical implications of identifying a pathogenic/likely pathogenic *PTEN* variant in a child with severe macrocephaly. In pediatric practice, rapidly progressive head growth should prompt consideration of genetic causes. In our case, conventional causes of macrocephaly were excluded, and the molecular testing of PTEN with the identification of likely pathogenic variant-c.377C>G p. (Ala126Gly) proved decisive. Functional studies have demonstrated that this mutation is neomorphic, altering PTEN's lipid phosphatase activity and shifting it toward a 5-phosphatase function, thereby increasing PI3K/AKT signaling and enhancing cellular migratory capacity [3]. This mechanism may carry distinct oncogenic implications compared to classical loss-of-function variants. Clinical data confirm that children with *PTEN* mutations frequently present with macrocephaly, café-au-lait-like spots, and variably with developmental delay or autism spectrum disorder. Hansen-Kiss *et al*. reported high rates of thyroid and gastrointestinal involvement, including hamartomatous polyps, even in childhood [4]. Consequently, surveillance must start early and adapt as manifestations evolve with age. Additionally, the identification of this *PTEN* variant may enable the use PI3K/AKT pathway inhibitors as the most pertinent targeted therapies for tumors eventually detected [5].

International consensus guidelines recommend structured follow-up, including annual thyroid ultrasound from early childhood, dermatological and developmental assessments, and careful monitoring for gastrointestinal symptoms, which should prompt timely endoscopic evaluation. From adolescence, renal imaging and breast/gynecologic surveillance in females are introduced, while colonoscopic screening is initiated by the mid-30s or earlier in symptomatic cases [6]. For pediatricians, the challenge lies in recognizing macrocephaly as a potential sentinel sign of PHTS and ensuring long-term multidisciplinary care.

Conclusion

This case of severe pediatric macrocephaly associated with a neomorphic *PTEN* variant highlights the importance of integrating genetic testing into the diagnostic work-up. Early recognition enables appropriate surveillance for cancer risk and other systemic manifestations, even in asymptomatic children, proper genetic counseling with identification of at risk relatives, and eventually targeted therapies in case of neoplasm detection. For pediatricians, awareness of PHTS is essential to guide timely referral, family counseling, and long-term follow-up strategies that may significantly alter prognosis.

References

1. Accogli A, Geraldo AF, Piccolo G, Riva A, Scala M, Balagura G, *et al*. Diagnostic approach to macrocephaly in children. Front Pediatr. 2022 Jan 14;9:789069. Available from: https://pubmed.ncbi.nlm.nih.gov/35096710/
2. Yehia L, Keel E, Eng C. The clinical spectrum of PTEN mutations. Annu Rev Med. 2020;71:103-116. Available from: https://pubmed.ncbi.nlm.nih.gov/31433956/
3. Costa HA, Leitner MG, Sos ML, Mavrantoni A, Rychkova A, Johnson JR, *et al*. Discovery and functional characterization of a neomorphic PTEN mutation. Proc Natl Acad Sci U S A. 2015 Nov 10;112(45):13976-13981. Available from: https://pubmed.ncbi.nlm.nih.gov/26504226/
4. Hansen-Kiss E, Beinkampen S, Adler B, Frazier T, Prior T, Erdman S, *et al*. A retrospective chart review of the features of PTEN hamartoma tumour syndrome in children. J Med Genet. 2017 Jul;54(7):471-478. Available from: https://jmg.bmj.com/content/54/7/471
5. Polivka J, Janku F. Molecular targets for cancer therapy in the PI3K/AKT/mTOR pathway. Pharmacol Ther. 2014;142(2):164-175. Available from: https://pubmed.ncbi.nlm.nih.gov/24333502/
6. Dhawan A, Baitamouni S, Liu D, Yehia L, Anthony K, McCarther A, s Cancer and overgrowth manifestations of PTEN hamartoma tumor syndrome: management recommendations from the International PHTS Consensus Guidelines Working Group. Clin Cancer Res. 2025 May 1;31(9):1754-1765. Available from: https://aacrjournals.org/clincancerres/article/31/9/1754

How to Cite This Article
Ferraz SC, Santos Nobre M, Sousa Fernandes S, Gonçalves-Rocha A, Costa M. Severe macrocephaly and PTEN likely pathogenic variant p.(Ala126gly): A case report. International Journal of Pediatrics and Neonatology. 2026;8(1):19-21.