Macrocephaly/autism syndrome exhibits neuroradiological abnormalities including Arnold-Chiari syndrome type I: Clinico-radiological spectrum of a *PTEN*-opathy

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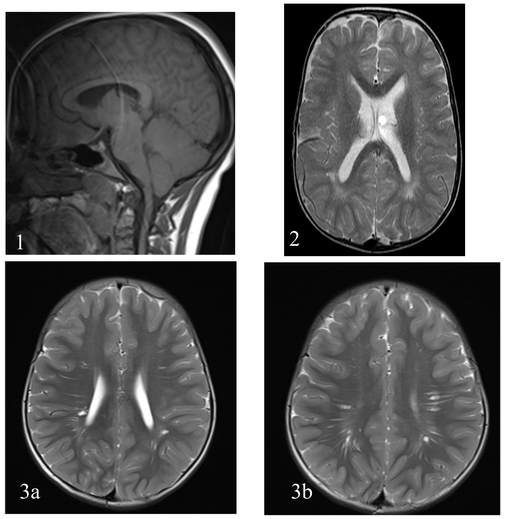
PTEN (phosphatase and tensin homologue) gene on chromosome 10q23.31 encodes a tumor suppresor protein which is mainly essential for cell-cycle regulation, angiogenesis, and cellular growth and proliferation. *PTEN*'s major role is in the inhibition of AKT via the phospoinositide 3-kinase (PI3-K)/AKT pathway. The term *PTEN*-opathy has been proposed to explain the phenotypic spectrum from overgrowth to malignancy which can occur when PTEN or its pathway molecules malfunction. Germline pathogenic variants in the *PTEN* tumor supressor gene cause a number of disorders including Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome, and autism spectrum disorders with macrocephaly. The umbrella term *PTEN* hamartoma tumor syndrome refers to these clinical entities.

OBJECTIVES

Macrocephaly/autism syndrome caused by heterozygous variants in the *PTEN* gene is characterized by increased head circumference, autism spectrum disorder, and/or developmental delay. All patients with molecularly proven PTEN pathogenic variants are at increased risk of developing benign or malignant tumors. Early diagnosed patients may benefit from cancer surveillance strategies. Neuroradiological features combined with clinical abnormalities might help to provide an earlier diagnosis in children. Therefore we aim to present clinical and neuroradiological data on children with macrocephaly/autism syndrome with an emphasis on a novel variant in the *PTEN* gene.



METHODS

We retrospectively collected clinical and neuroradiological information and molecular diagnosis data from eight pediatric patients with macrocephaly/autism syndrome. This study was performed in accordance with the Declaration of Helsinki and with the approval of the ethics committee of the institution. Specific gene testing or whole-exome sequencing was performed to identify causal variations in the *PTEN* gene. Blood samples were obtained from the patients and their parents after receiving informed consent. Variant classification was performed according to 2015 ACMG/AMP sequence variant interpretation guidelines.

RESULTS

All the patients had macrocephaly with developmental delay/intellectual disability and autism spectrum disorder had been diagnosed in five of them. Six patients had pathogenic variants, whereas two patients had likely pathogenic variants. The spectrum of *PTEN* variants identified included deletion, intronic splicing, missense, nonsense, and non-coding variants. The novel variant was an inframe deletion variant; the patient with this variant had obesity and had been diagnosed with generalized epilepsy. Two patients had thyroid abnormalities, one with hypoechoic nodules and the other with colloidal cysts. Neuroradiologically, one patient had Arnold-Chiari type I malformation (figure 1), three had periventricular hyperintensities on T2-weighted images (figure 2) and one had dilated perivascular spaces (figure 3a, b). A skin lesion was present in one patient as a hypomelanotic macule.

DISCUSSION

We reported on a group of patients with PTEN pathogenic variants who exhibited neuroradiological abnormalities like static periventricular hyperintensities, dilated perivascular spaces and Arnold-Chiari type 1. Although these may accompany other disorders such as mucopolysaccharidoses, Lowe syndrome and hypomelanosis of Ito, we believe in the appropriate clinical context these MRI patterns may prompt consideration of the diagnosis of a *PTEN*-opathy.

CONCULSIONS

Although non-specific, neuroradiological abnormalities like periventricular hyperintensities, dilated perivascular spaces, and Arnold-Chiari type I may constitute a clue for the early diagnosis of macrocephaly/autism syndrome. Obesity and epilepsy infrequently accompanied this form of *PTEN*-opathy in our case series.

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