

# Hemimegalencephaly with Bannayan-Riley-Ruvalcaba syndrome

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**ABSTRACT** – Hemimegalencephaly is known to occur in Proteus syndrome, but has not been reported, to our knowledge, in the other *PTEN* mutation-related syndrome of Bannayan-Riley-Ruvalcaba. Here, we report a patient with Bannayan-Riley-Ruvalcaba syndrome who also had hemimegalencephaly and in whom the hemimegalencephaly was evident well before presentation of the characteristic manifestations of Bannayan-Riley-Ruvalcaba syndrome. An 11-year-old boy developed drug-resistant focal seizures on the fifth day of life. MRI revealed left hemimegalencephaly. He later showed macrocephaly, developmental delay, athetotic quadriplegic cerebral palsy, and neuromuscular scoliosis. Freckling of the penis, which is characteristic of Bannayan-Riley-Ruvalcaba syndrome, was not present at birth but was observed at 9 years of age. Gene analysis revealed a c.510 T>G *PTEN* mutation. This patient and his other affected family members, his father and two siblings, were started on the tumour screening procedures recommended for patients with *PTEN* mutations. This case highlights the importance of early screening for *PTEN* mutations in cases of hemimegalencephaly not otherwise explained by another disorder, even in the absence of signs of Proteus syndrome or the full manifestations of Bannayan-Riley-Ruvalcaba syndrome.

**Key words:** hemimegalencephaly, *PTEN* mutation, Bannayan-Riley-Ruvalcaba syndrome, Proteus syndrome

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Hemimegalencephaly (HME) is defined as hamartomatous overgrowth limited to one cerebral hemisphere, usually resulting in the clinical phenotype of intractable epilepsy, severe psychomotor retardation, and contralateral hemiparesis (Flores-Sarnat, 2002). Bannayan-Riley-Ruvalcaba syndrome

(BRRS) is a congenital disorder characterized by macrocephaly, pigmented macules of the glans penis, lipomas, and intestinal hamartomas (Eng, 2016). Here, we describe an association between the two that, to our knowledge, has not been reported in the literature before.

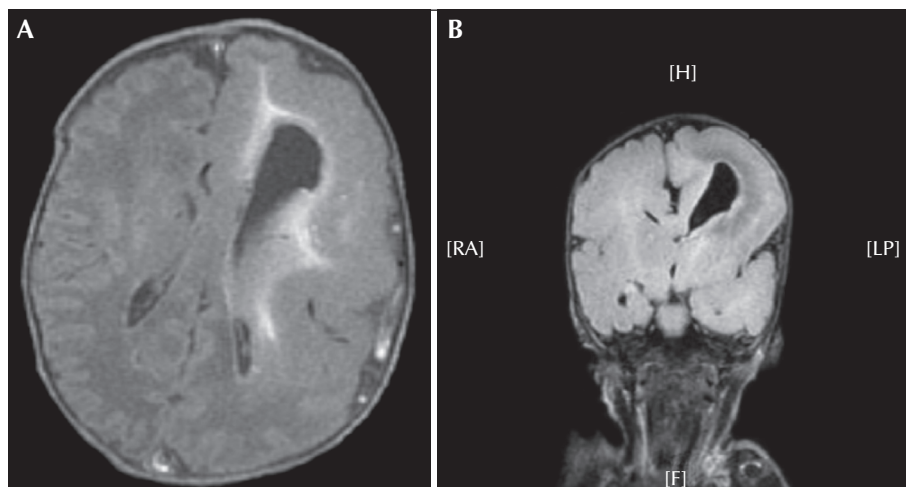
## Case study

Our patient was born at 32 weeks gestation by elective C-section due to polyhydramnios and suspected hydrocephalus. On Day 5 of life, he developed seizures consisting of tonic elevation of the arms with nystagmus and mouth twitching and apnoea, managed in an outside hospital, where an MRI, performed at 14 days of age, revealed left hemimegalencephaly (figure 1). Because of ongoing seizures, 1-2 times per day, he was transferred to our hospital at the age of 3.5 weeks. At that time, EEG showed a bilateral burst-suppression pattern with higher amplitudes and more sharp activity on the left, as compared to the right. Seizures were not controlled despite trials of several antiepileptic medications, including phenobarbital, levetiracetam, clonazepam, and topiramate. The seizures gradually increased in frequency, reaching 15-20 a day, requiring the patient to undergo left functional hemispherectomy at 4 months of age, after which seizures resolved (the MRI after hemispherectomy is presented in figure 2). Pathological examination revealed cortical dysplasia in the left lateral and medial temporal lobe and severe cortical dysplasia in the left frontoparietal lobe. Head circumference, which had been within the 90<sup>th</sup> percentile (40 cm) at one month of age, gradually increased to reach the 99<sup>th</sup> percentile (53 cm) at 7 months of age. The patient was seizure-free until the age of 2 years when he started to have seizures from the other hemisphere. He has been trialled on several medications, but his seizures have continued to be drug resistant. The patient is the second of four sons in his family. When the patient was 6 years of age, his younger brother was evaluated in the Genetics Clinic for macrocephaly and had developmental delay, autism

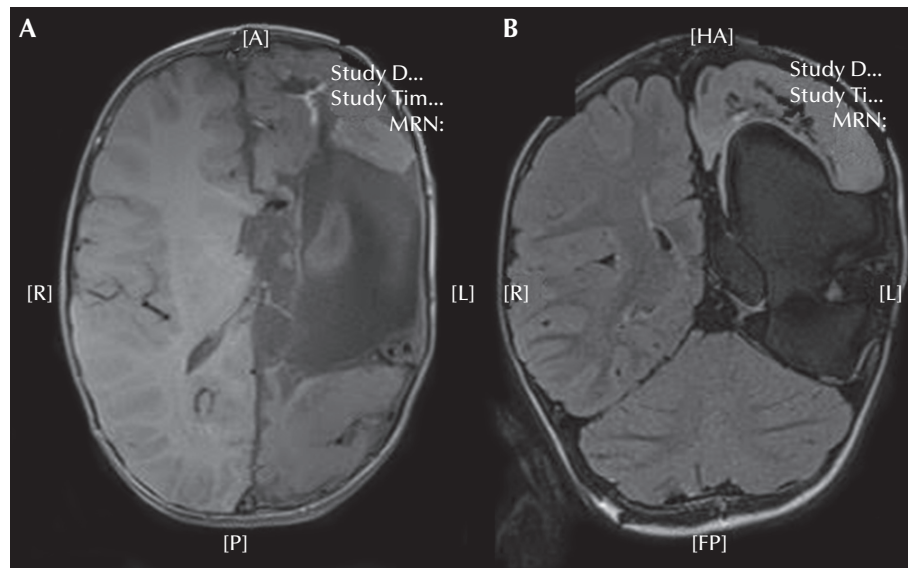
spectrum disorder, freckling of the penis, and febrile seizures, thus fitting the diagnosis of Bannayan-Riley-Ruvalcaba syndrome. Gene analysis revealed a heterozygous paternally inherited *PTEN* mutation resulting in c.510 T>G substitution, leading to substitution of serine for arginine at amino acid position 170 (S170R) (NM\_000314.6) (OMIM # 601728), and a maternally inherited duplication of chromosome 911p.21 involving the *TJP2* (Tight Junction Protein 2) gene. Cascade testing on his siblings revealed this mutation in our patient and the youngest brother, who had macrocephaly but was otherwise asymptomatic.

At the time of diagnosis of the brother, our proband was 6 years old and was diagnosed with autism spectrum disorder, had global developmental delay, was wheelchair-bound, and was able to feed himself with his hands but could not use a spoon or fork, and was mostly non-verbal but able to follow commands. He had macrocephaly, choreoathetosis, and neuromuscular scoliosis. Examination at nine years showed multiple hyperpigmented lesions over the glans penis and a *café au lait* macule on the arm, not present on previous examinations.

The father, who has the same mutation, has macrocephaly and a history of a seizure disorder but was not available for further examination. The mother was asymptomatic. On further investigation of the family history, our patient's father has a twin brother with macrocephaly, thyroid nodules, and thyroidectomy due to thyroid cancer, and another brother who may have had anencephaly based on the description provided by the family. Mitochondrial DNA was also analysed and revealed no mutations. To rule out an alternative aetiology for the seizures in our patient with hemimegalencephaly, whole-exome sequencing was performed but did not reveal any suggestive



**Figure 1.** (A) Axial FLAIR view and (B) Coronal T1 view of the patient's brain MRI during infancy showing left hemimegalencephaly, lissencephaly, and left periventricular white matter abnormalities.



**Figure 2.** (A) Axial T1 and (B) Coronal FLAIR view of the patient's brain MRI after left hemispherectomy.

mutations. We also searched for modifier genes that may explain the well-known intrafamilial variability seen in families with Phosphatase and tensin homolog (PTEN), but no such genes were found.

Following the screening guidelines provided by the National Comprehensive Cancer Network (Eng, 2016), we are performing annual dermatological and annual thyroid ultrasounds on all three brothers. Our patient was found to have three hyperechoic, slow-growing nodules in the right thyroid gland; the younger 8-year-old brother had a normal examination, and hyperemic sub-centrimetric nodules were present in the left thyroid of the youngest 7-year-old brother. As these lesions are not suggestive of malignancy, annual surveillance will be continued.

## Discussion

### Bannayan-Riley-Ruvalcaba syndrome and PTEN tumour hamartoma syndrome

The phenotype of our case fits the clinical picture of Bannayan-Riley-Ruvalcaba syndrome (BRRS). Parisi *et al.* indicated that at least two of the following criteria should be present to establish the diagnosis: macrocephaly, intestinal hamartomas, and penile macules in boys. They also reported a patient who did not have speckling of the penis at age 4 years, but developed these macules three years later, indicating that a diagnosis of Bannayan-Riley-Ruvalcaba should not be dismissed early in life. Their case illustrates a similar series of events as seen in our patient,

but with no hemimegalencephaly in their patient (Parisi *et al.*, 2001).

BRRS is one of four diseases that fall under the umbrella of PTEN hamartoma tumour syndrome (PHTS). The other three are: Cowden syndrome (CS), which has a delayed onset usually in the third decade of life, consisting of mucocutaneous lesions (trichilemmomas and papillomatous papules), hamartomatous and mixed gastrointestinal polyps, macrocephaly, and dolicocephaly; Proteus syndrome, which is an overgrowth syndrome affecting various organ systems and develops rapidly and suddenly during childhood; and Proteus-like syndrome, which is the term that describes individuals who meet some but not all the diagnostic criteria for Proteus syndrome (Eng, 2016) (table 1). Of note, the risk of malignant tumours of the thyroid, breast, and endometrium is especially high with CS. Nevertheless, any individual found to have a *PTEN* mutation must be treated as a high-risk patient with regards to malignancy and the screening recommendations for CS must be applied (Eng, 2016).

### Hemimegalencephaly in association with BRRS and PHTS

Our literature review of PHTS revealed that, in the scope of PHTS, hemimegalencephaly has been reported almost exclusively in association with Proteus syndrome. Only one case did not fit the phenotype of Proteus syndrome. This was the case of a newborn male with an asymmetric skull bulging to the left, ipsilateral linear nevi on the nose and forehead, and intractable seizures which led to his demise on Day 3 of life (Merks *et al.*, 2003). The phenotype of the

**Table 1.** Clinical manifestations of Proteus syndrome and Bannayan-Riley Ruvalcaba syndrome and their presence in our patient, his siblings, and his father.

Manifestations	Proteus Syndrome	Bannayan-Riley-Ruvalcaba Syndrome	Patient	8-year-old brother	7-year-old brother	Father
Macrocephaly	+/-	+	✓	✓	✓	✓
Lipomas	+	+				
Hemangiomas	+	+				
Hamartomatous intestinal polyps	-	+				
Speckled penis	-	+	✓	✓		
Cerebriiform connective tissue nevi	+	-				
Distorting progressive overgrowth	+	-				
Epidermal nevi	+	-				
Ovarian cystadenoma	+	-				
Parotid adenoma	+	-				
Facial dysmorphism	+	-				
Autism spectrum disorder	-	+/-	✓	✓		
Developmental delay	+/-	+/-	✓	✓		
Hemimegalencephaly	+/-	-	✓			
Seizures	+/-	-	✓			✓
Scoliosis	+/-	+/-	✓			
Strabismus	+/-	+/-	✓			

+: Major manifestation; +/-: May or may not be present; -: Not present; ✓: Individual fulfils this criterion.

latter case suggested the clinical diagnosis of Jadassohn nevus sebaceous syndrome, however, genetic analysis revealed that he had *PTEN* mutation IVS5+1delG (Merks *et al.*, 2003). Our case is unique in that it provides further evidence that hemimegalencephaly may be found in cases of PHTS other than Proteus syndrome. We encourage clinicians to consider this diagnosis in hemimegalencephalic patients who do not meet the criteria for the diagnosis of Proteus syndrome and order the necessary genetic testing. Early intervention in cases of *PTEN* mutation has the potential to prevent drastic consequences, most notably the development of malignancy.

### Phenotypic variability in our family

The mutation described in this family has previously been reported in a family diagnosed with BRRS presenting with macrocephaly, speckled penis, and

soft tissue tumours including lipomas, hemangiomas, and leiomyomas (Marsh *et al.*, 1997). It has also been implicated in the development of invasive ductal carcinoma in CS (Banneau *et al.*, 2010). *PTEN* gene mutations have been reported to be 100% penetrant by early adulthood, but variably expressed (Mester *et al.*, 2015). This may explain the phenotypic variability within the family described here and the fact that HME was observed in only one child.

### Epileptic manifestations of BRRS

To our knowledge, seizure disorders have not been reported in association with Bannayan-Riley-Ruvalcaba syndrome. Our patient manifested a seizure disorder due to his hemimegalencephaly, which is a structural brain malformation. His seizures are best characterized as focal motor seizures with automatisms. While epileptic manifestations in patients

with HME vary considerably, the most commonly observed seizure type is focal, and the seizures are usually refractory to medical management (Flores-Sarnat, 2002). This is similar to what we observed in our patient.

### Potential underlying molecular mechanism for hemimegalencephaly

PHTS and HME appear to be related molecularly at the level of the PI3K-AKT-mTOR pathway, thus providing a molecular explanation for our observation of HME in BRRS (Waite and Eng, 2002). *PTEN* mutations lead to dephosphorylation of PIP3, thus decreasing the translocation of the AKT3 protein to the cell membrane and enhancing apoptosis (Waite and Eng, 2002). Thus, loss-of-function mutations of the *PTEN* tumour suppressor gene can be expected to result in unregulated cellular proliferation, contributing to the development of HME. D’Gama et al. also reported seven patients with HME with germline missense mutations in the *DEPDC5*, *MTOR*, *PIK3CA*, and *TSC2* genes. They suggested the hypothesis of a “second hit” mutation leading to focal symptoms of HME (D’Gama et al., 2015). We conclude that HME can occur in the context of BRRS and that our case highlights the importance of screening for *PTEN* mutations early in cases of HME not explained by another disorder, even in the absence of Proteus syndrome clinical manifestations or the full manifestations of BRRS. □

### Supplementary data.

Summary didactic slides are available on the [www.epilepticdisorders.com](http://www.epilepticdisorders.com) website.

### Disclosures.

None of the authors have any conflict of interest to declare.

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## TEST YOURSELF



- (1) What are the causes of Bannayan-Riley-Ruvalcaba syndrome?
- (2) What are the screening recommendations for child patients with *PTEN* mutations?
- (3) Which syndromes are associated with hemimegalencephaly?

*Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, [www.epilepticdisorders.com](http://www.epilepticdisorders.com), under the section “The EpiCentre”.*