Dear Editor,

Bannayan-Riley-Ruvalcaba syndrome (BRRS) classically presents with macrocephaly, subcutaneous and visceral lipomata, haemangiomata, hamartomatous intestinal polyps and pigmented macules involving the genitalia. This autosomal dominant disorder is linked to germline mutations of the phosphatase and tensine homologue gene (PTEN), a tumour suppressor gene which has a significant role in the molecular pathway of cellular proliferation, migration and apoptosis. We report a paediatric patient with macrocephaly and multiple benign tumours who had a nonsense mutation of PTEN.

Case Report

A 7-year-old Chinese girl was referred for evaluation of macrocephaly, multiple benign tumours and multiple pigmented skin lesions (Fig. 1). On retrospect, newborn screening revealed that her head circumference was 38.5 cm (>98th percentile); she had a wide anterior fontanelle with normal sutures. She had frontal bossing and hypertelorism; tomography (CT) scan at 1 month of life showed mild dilatation of the lateral ventricles; there were no other brain abnormalities. Her developmental milestones were normal. She was treated with subcutaneous triamcinolone for the haemangioma, followed by laser therapy at 12 months as it continued to increase in size.

At 3 years of age, she developed a lipoma on her left thigh. She underwent tonsillectomy at 6 years as she had features of upper airway obstruction; histopathologic examination (HPE) of the tonsillar swelling showed non-malignant reactive lymphoid hyperplasia. She also had excision of a thyroid nodule, which was found incidentally, 6 months following tonsillectomy. Clinically, she was euthyroid and HPE confirmed a diagnosis of follicular adenoma.

There was no significant family history of note. She is the youngest of 3 siblings. Her older brother who is 16 years old has a pigmented macule over the left shoulder but none over the penile area. PTEN was subject to mutation screening by Dideoxy DNA sequencing and Multiplex Probe Ligation Amplification analysis to determine if mutations occurred within reading frame of the gene. DNA sequencing was performed on a semi-automated sequencing unit (model 3730, Perkin-Elmer Applied Biosystems Division, Foster City CA) according to the manufacturer’s instructions. Mutation analysis of PTEN in our patient revealed a novel nonsense mutation: the “T” insertion at position c.865_866 has created a frameshift at codon 289 resulting in a premature stop 9 codons downstream.

Discussion

The clinical entity comprising macrocephaly, pseudopapilloedema and haemangiomata was first reported in 1960 by Riley and Smith. Following this, several other reports were made which subsequently included features such as multiple lipomata, intestinal hamartomatous polyps, pigmented spotting of the penis and mental retardation. A mutation in the PTEN gene has been implicated in between 50% to 60% of BRRS. These mutations range from single base nucleotide substitutions to gross deletions and insertions. To date, there are more than 80 reported mutations in the missense and nonsense category; the mutation in our patient was identified at codon 289 causing a premature stop.

Fig. 1. Frontal appearance of patient.
Recent reports have now shown that Cowden syndrome (CDS) and BRRS are allelic disorders at the PTEN locus on chromosome 10q23. It has been reported that some BRRS cases eventually develop features of CDS at an older age. In view of the clinical and genetic overlap, BRRS and CDS are now accepted as different phenotypic expressions of the same allelic syndrome and thus are collectively referred to as PTEN hamartoma-tumour syndrome.4

BRRS represents an overgrowth syndrome; macrocephaly (defined by a head circumference above the 95th percentile) is observed in all cases and persists into adulthood. Ventricular size is usually normal. Macrocephaly was present in our patient from birth. Although ventriculomegaly was noted, it was of no clinical significance as the child had no neurological deficit and had normal cognitive function. Mental retardation is however reported in between 20% to 50% of BRRS patients. In fact, it is often suggested that BRRS should be excluded in patients who present with both macrocephaly and developmental delay. Abnormal facial features include frontal bossing, hypertelorism, down-slanting palpebral fissures, depressed nasal bridge, strabismus, epicanthus inversus, small beaked nose, long philtrum, thin upper lip, broad mouth and relative micrognathia.5 Most specific for the syndrome however is presence of pigmented maculae on the glans penis that occur in most male patients. These are subtle, and must be looked for specifically. The first 4 facial features are seen in our proband; although genital lentigines was not seen in her brother, the presence of an isolated pigmented macule should not be dismissed too readily. This is because variable expressivity is a recognised phenomenon in diseases with autosomal dominant inheritance. With identification of the mutation in his sister, predictive genetic testing is now an option for her family members.

More than 50% of patients have a history of multiple benign tumours. The tumours which tend to enlarge rapidly may demonstrate local aggressive behaviour. They also tend to not resolve spontaneously.3 This feature is reflected in our patient where laser treatment was required for the facial haemangiomata. This is in contrast to normal circumstances where spontaneous resolution is the general rule. Our patient also had a history of thyroid adenoma. This is interesting because up to 31% of BRRS patients have thyroid involvement in the form of multinodular goitre, thyroid adenoma or thyroid cancer. Hamartomatous polyps occur in 35% to 40% of the patients and are located in the gastrointestinal tract.5 Annual surveillance starting from childhood, with a haemoglobin level and faecal occult blood test may thus be useful in the early diagnosis of polyposis.5 In addition to this, periodic surveillance for other related tumours are indicated in PTEN mutation positive BRRS patients as recommended in those diagnosed to have CDS.

A multi-disciplinary approach is warranted in patients diagnosed with BRRS as there is multi-systemic organ involvement. As the clinical expression is highly variable and unpredictable, a careful search for other affected family members should ideally be carried out as not only is the recurrence risk for future offspring high, but particularly because of the risk of developing tumours, both benign and malignant. Needless to say, genetic counselling and predictive genetic testing form an important component in the management strategy of such families.

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REFERENCES


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