

# A Rare Cause of Glans Penis Pigmentation: Bannayan-Riley-Ruvalcaba Syndrome

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## Abstract

Bannayan-Riley-Ruvalcaba syndrome is a rare condition caused by mutation in the *PTEN* gene. It can cause pigmentation defects, hamartoma and behavioural abnormalities. We report the case of a 10-year-old boy with short stature, pigmented maculae on the glans penis, obsessive-compulsive disorder and macrocephaly. The case is presented due to the rarity of the condition and its predisposition to tumour formation.

## Key words

Pigmentation; *PTEN*; Tumour

## Introduction

Bannayan-Riley-Ruvalcaba syndrome (BRRS) is an overgrowth syndrome and part of a rare spectrum characterised by macrocephaly, glans penis pigmentation and benign hamartomatous formation. It occurs through mutations in the phosphatase and the tensin homolog gene (*PTEN*). This is a tumour suppressor gene that plays an important role in cell proliferation, migration and apoptosis. Its tumour suppressor activity derives from lipid phosphatase

activity. Mutations in this tumour suppressor gene lead to various clinical syndromes, such as Bannayan-Riley-Ruvalcaba, Cowden syndrome and autism accompanied by macrocephaly.<sup>1</sup> These autosomal dominant syndromes, known as *PTEN hamartoma tumour syndrome* (PHTS), are significant because of their predisposition to cancer. Proteus syndrome and Cowden syndrome are entities deriving from age-related expression of the same condition. BRRS is a rare syndrome characterised by macrocephaly, subcutaneous and visceral lipomas, haemangiomas, hamartomatous intestinal polyps and pigmented macules in the genital region.<sup>2</sup> Following examination we suspected BRRS in a patient presenting due to short stature. This report is intended to emphasize the need for awareness of this entity due to potential subsequent tumour development.

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## Case

A male patient aged 10 years and 3 months presented to our clinic due to short stature. The patient had been born by Cesarean delivery weighing 3250 g and experienced no health problems until the age of 5 years, apart from a large head circumference noted by the family. The father was not alarmed due to his own history of shortness of stature at primary school age followed by subsequent catch-up in growth. There was no observation of haemangioma and a broad anterior fontanel in infancy, or of palpable lipoma. However, head circumference was at upper limits from

infancy onward. Computed tomography of the brain revealed no pathology, and the patient was placed under monitoring. No members of the family had macrocephaly or abnormal skin pigmentation.

At physical examination at presentation, the patient's height was 129 cm (-2.19 SDS), weight 27 kg (-1.74 SDS) and head circumference 54 cm (2.55 SDS). Genetic height potential was 175 cm. The patient exhibited marked frontal bossing and macrocephaly. Bilateral strabismus was present, and both thumbs were enlarged. Genital examination revealed bilateral testis dimensions of 3 ml and a stretched penile length of 4.5 cm. Brown macular pigmentation was observed on the glans (Figure 1).

Haematological and biochemical parameters were within normal limits.

Growth hormone IGF-1 axis, thyroid hormones and thyroid autoantibodies were within normal ranges. BRRS was suspected due to macrocephaly, strabismus and the pigmented glans penis. Ultrasound of the abdomen and thyroid was normal. The fecal occult blood (FOB) test performed for possible intestinal and colonic hamartomas resulted negative. However, colonic and small bowel imaging were not performed. Neurological examination was normal, and the patient exhibited no developmental retardation. However, he exhibited widespread anxiety and obsessions evaluated as falling within the autistic spectrum and was referred for pediatric psychiatric observation. Genetic testing could not be performed for financial reasons.

## Discussion

Comorbidity of macrocephaly, pseudopapilledema and haemangioma was first reported by Riley and Smith in 1960,<sup>3</sup> since when cases with multiple lipomas, intestinal polyps, pigmented patches on the penis and mental retardation have also been reported.<sup>4</sup>

BRRS is a *PTEN hamartoma syndrome*, and mutation in the *PTEN* gene is observed at levels of 50-75%. These mutations may be associated with a single base change or may emerge following major deletions and insertions. Some 80 mutations have been reported to date, the most common being stop codon mutations in the 289th codon. This mutation may also give rise to Cowden syndrome. These two conditions are therefore described as allelic diseases. *PHTS* is the common name for these two conditions, but refers to different age-dependent entities. Some patients with BRRS identified with mutations in the 10q23 region of the *PTEN* gene are eventually diagnosed with Cowden

syndrome. These syndromes with clinical and genetic overlap are not distinct, but are rather the same allelic syndromes deriving from differing phenotypic expressions.<sup>1</sup> Macrocephaly is determined in 100% of *PTEN*-positive cases, developmental retardation in 93% and glans penis pigmentation in 85%.<sup>4,5</sup>

Although BRRS is an overgrowth syndrome, with the exception of macrocephaly there was no retardation in our patient's other anthropometric measurements compared to his age group. The patient's history indicated macrocephaly since birth, but this was not a familial characteristic. Computed tomography was compatible with ventriculomegaly. Even in cases with ventriculomegaly there may be no mental retardation or significant neurological deficit. However, some studies have reported mental retardation levels of between 20% and 50%.<sup>1</sup> Marked anxiety disorder was determined in our patient. The subject was referred for psychiatric observation, and this condition was evaluated as a component of the syndrome.

Frontal bossing, hypertelorism, a downslanting palpebral fissure, a depressed nasal bridge, strabismus, epicanthus inversus, a small beaked nose, a thin upper lip and relative micrognathia are phenotypic characteristics of the syndrome<sup>5</sup> and were also present in our patient. Every syndrome has its own indicative findings, and glans penis pigmentation is a specific indicative entity in this syndrome. However, it may sometimes not be detected, and the families of affected individuals should also be screened. In our case, the mother had noticed cutaneous involvement in



**Figure 1** Pigmentation on the glans penis.

the form of glans penis pigmentation from the age of 5 years, but the condition was not present in the other brothers.

There are no internationally agreed criteria for the diagnosis of BRRS, although Marsh et al suggested that three out of macrocephaly, pigmented macules, lipoma and haemangioma are sufficient for diagnosis.<sup>6</sup> Parisi et al however, suggested that two out of hamartoma, macrocephaly and glans penis pigmentation are sufficient.<sup>4</sup> BRRS was diagnosed in our case with the observation of two entities.

When *PTEN hamartoma syndrome* affect children, macrocephaly, varying degrees of developmental retardation, intellectual disability, autism spectrum disease, pigmented penile macules, vascular anomalies and hamartomas may be observed. Of these, macrocephaly is generally the most common component of the syndrome. Intellectual and developmental retardation is one of the most widespread findings. This syndrome should be considered if accompanied by macrocephaly, and an individual approach should be planned. The syndrome was suspected in our case due to the indicative finding, glans penis pigmentation, accompanied by macrocephaly. Pigmented penile macules are another indicative finding in this syndrome. This was determined in all males in one series of 82 cases. It may also occur subsequently even if not present at birth. Genital examination must be carefully performed from that perspective.<sup>7</sup> The presence of macules on the glans penis in our case prompted more detailed examination.

Tumoural formation's that can occur in the thyroid, small bowel and colon are also indicative in this syndrome and require assessment at specific intervals. Thyroid adenoma

or cancer is seen in 1/3 of reported cases, and hamartomatous polyps in the gastrointestinal tract may also be observed in approximately 1/3 cases. Renal cell cancer has even been reported.<sup>8</sup> Physicians must be alert to this possibility. Thyroid and abdominal USG were normal in our case, and FOB investigated for potential gastrointestinal system involvement was negative. However, such cases must be closely monitored with annual follow-ups. Although some cases may be diagnosed with pronounced characteristics, others may exhibit very mild clinical involvement. Since this clinical entity derives from mutation in a tumour suppressor gene, routine blood count, urinary examination, abdominal and thyroid USG, FOB and colon imaging together with magnetic resonance of the brain due to the risk of cranial tumour should be performed twice a year.<sup>9,10</sup> This surveillance protocol is shown in Table 1.

One study investigating the incidence of tumour reported that the youngest patient out of 34 cases of *PTEN* hamartoma syndrome with genetically proven diagnosis was 2 years old, and that thyroid carcinoma was seen in four cases, renal cell cancer in one and ovarian granula cell tumour in one. Lipoma was determined in 40 of this cohort.<sup>5</sup>

Although it is a rare entity, BRRS should be considered in cases with macrocephaly, glans penis pigmentation and behaviour disorder. In addition, since it is one of the syndromes that predispose to cancer, patients should be followed-up annually.

### Declaration of Interest

None

**Table 1** Protocol for surveillance in *PTEN*-mutation positive BRRS cases (Reference 10)

	Methods	Frequency	From age
Breast cancer, Female	Self-examination	Monthly	25
	Clinical examination	Annual	25
	Mammography	Annual	35
Breast cancer, Male	Self-examination	Monthly	25
Endometrial cancer, Female	Biopsy	Yearly	35-menopause
	Transvaginal ultrasound		Menopause
Thyroid cancer, Female and male	Palpation	Yearly	18
Renal cancer, Female and male	Urinalysis	Yearly	
Hamartomas of the bowel, Females / males	Blood test: Haemoglobin level	Yearly	Early Infancy
	Colonoscopy once		At age 50

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