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Acromegaly in the setting of Tatton-Brown-Rahman Syndrome

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Abstract

Purpose Tatton-Brown-Rahman syndrome (TBRS) is a newly defined genetic entity characterized by overgrowth and intellectual disability, resulting from germline mutations in the gene encoding DNA methyltransferase 3 alpha (DNMT3A). Affected individuals with benign and malignant tumors have been reported; to our knowledge pituitary adenomas (and other tumors identified in our patient) have not yet been described in this syndrome.

Case We report the case of a 34-year-old woman with TBRS who developed a GH-secreting pituitary macroadenoma and other benign tumors and cystic lesions involving diverse organ systems. Whole-exome sequencing revealed a heterozygous, likely pathogenic variant (c.700_709 del10, p. Gly234ArgfsX79) in exon7 of *DNMT3A*, and a heterozygous variant of uncertain significance (c.25 C>T, p.Arg9Trp) in exon 1 of the gene encoding aryl hydrocarbon receptor-interacting protein (*AIP*). The patient failed somatostatin analog treatment, and underwent surgery. The tumor retained AIP expression, and analysis of tumor DNA indicated the presence of both *AIP* alleles, consistent with no loss of heterozygosity. These findings suggest that the *AIP* variant was not the primary driver of pituitary adenoma development.

Conclusion Our case suggests that TBRS might be associated with pituitary adenoma and a broader spectrum of tumors than previously thought, making long-term follow up of these patients crucial to identify tumors early, and to elucidate the clinical spectrum of the disorder for optimization of management.

Keywords Tatton-Brown-Rahman syndrome (TBRS) · Pituitary adenoma · Overgrowth · Aryl hydrocarbon receptor interacting protein (AIP) · Growth hormone (GH) · DNA methyltransferase 3 alpha (DNMT3A)

Introduction

Tatton-Brown-Rahman syndrome (TBRS, MIM 615879) was initially described in 2014 when 13 individuals with a common phenotype of overgrowth and intellectual disability were found to have de novo heterozygous germline variants in the gene encoding DNA methyltransferase 3 alpha (DNMT3A) [1]. A family of DNA methyltransferase enzymes, including DNMT3A, mediates DNA methylation, an epigenetic modification important in development and disease. DNMT3A in particular is essential for establishing DNA methylation and imprinting in embryogenesis [2]. Somatically acquired *DNMT3A* mutations have been implicated in several types of cancer, including hematologic malignancies, such as acute myeloid leukemia (AML) [2–5]. Individuals with TBRS have intellectual disability, generalized postnatal overgrowth involving height and/or head circumference, and a distinctive facial appearance, including low-set and thick horizontal eyebrows, narrow palpebral fissures, a round and coarse-appearing face, and in some cases

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prominent upper central incisors [2]. Additional clinical features may include joint hypermobility, obesity, hypotonia, kyphoscoliosis, seizures, and psychiatric issues [3]. TBRS is extremely rare with fewer than 100 individuals having been reported [1–7]. The vast majority of these individuals are children with few adults having been described. Of the adults reported in the literature, most are in their 20s with the oldest reported case being 54 years old [6]. Therefore, little is known about disease manifestations in adulthood.

Despite well-documented postnatal overgrowth, no data exists on the growth hormone (GH) status of these patients, and it is unknown whether GH dysregulation is at least partially responsible for the generalized overgrowth. Here, we report a case of an adult with TBRS who presented with a GH-secreting pituitary macroadenoma (and additional distinct tumors) with a heterozygous variant of uncertain significance in the aryl hydrocarbon receptor-interacting protein gene *(AIP*).

Case report

A 34-year-old African American woman was referred for a recently diagnosed GH-secreting pituitary adenoma after a physician family member noted that she had enlarged physical features of the face and hands. Abnormal serum IGF-1 (551 ng/ml; reference range 53–331 ng/mL) was recorded, and the diagnosis of acromegaly was confirmed by lack of suppression of GH by a 75 g oral glucose load, with nadir GH level of 5.1 ng/mL. Additionally, she had a mild increase in prolactin of 32.7 ng/mL (reference range 4.8–23.3 ng/mL). Magnetic resonance imaging (MRI) of the pituitary gland showed a macroadenoma of 14 mm (transverse) × 12 mm (anteroposterior) ×11 mm (craniocaudal).

She was born at 41 weeks gestation via Caesarean section due to breech presentation to non-consanguineous parents after an uncomplicated pregnancy. Her birth weight was 4.54 kg. She developed seizures at 8 months of age after an apneic episode requiring cardiopulmonary resuscitation but has been seizure-free for over 20 years. She was diagnosed with developmental delay at 5 years of age and currently has intellectual disability. She had a history of multiple benign tumors and cystic lesions including liver cysts/hemangiomas, adenomatous polyps of the colon, a breast cyst, and a collagenoma. She had developed a left ovarian torsion requiring oophorectomy and left ureterolysis, followed by a total hysterectomy. She also had a history of benign cystic mesothelioma of the peritoneum and fibrous dysplasia of the maxilla requiring excision. She had kyphoscoliosis, mitral valve prolapse, a history of pulmonary embolism following oral contraceptive use, and her family reported transient hyperthyroidism. She had no other pertinent endocrinological family history, other than tall stature with her father measuring 190.5 cm, and sister measuring 170.2 cm. Her mother's height is 165.1 cm. The calculated mid-parental height is 171.3 cm. The patient's mother and maternal grandmother had breast cancer with onset after age 50 years. A maternal first cousin had a history of developmental delay and myotonic dystrophy. The patient's father (now deceased) had a history of hypertension and pulmonary embolism. Little additional information is known regarding the paternal side of the family.

At presentation her height was 178 cm (> + 2 SD above the mean) with a weight of 80.7 kg. Head circumference was 58.5 cm (> + 2 SD above the mean), and she exhibited subtle dysmorphic features, including a full round face, thick eyebrows, narrow down-slanting palpebral fissures, highly arched palate, and full lips. Skin inspection revealed numerous lentigines on the face and trunk, multiple café-au-lait macules scattered mostly on the trunk, and several hamartomas following Blashcko's lines. Cutaneous biopsies of two lesions showed only coarse dermal collagen. She had pectus carinatum and broad laterally-deviated great toes with hypoplastic nails. An ophthalmological exam showed astigmatism and cortical cataract. Whole exome sequencing from peripheral blood DNA showed a likely pathogenic heterozygous variant (c.700_709 del10, p.Gly234ArgfsX79) in exon 7 of the *DNMT3A* gene, leading to the TBRS diagnosis. Additionally, a germline heterozygous variant of unknown significance in exon 1 of the *AIP* gene (c.25 C>T, p.Arg9Trp) was identified. Both genetic variants were absent in her mother and sister. Her father's DNA was not available.

Because her guardian initially refused surgery, she was started on monthly lanreotide gel injections, initially 90 mg and later increased to 120 mg. Despite the encouraging initial response, her GH and IGF-1 failed to normalize. Cabergoline 0.5 mg three times per week was added to the regimen and helped to achieve a near-normal IGF-1 level. However, cabergoline was discontinued due to the development of hallucinations and nightmares. She subsequently underwent transsphenoidal resection of the adenoma, with normalization of serum GH and IGF-1. Pathology confirmed a pituitary adenoma (Fig. 1a), and GH staining was diffusely positive (Fig. 1b). Prolactin staining was focally positive whereas ACTH was negative (data not shown). To evaluate AIP protein levels in the tumor tissue, a specimen from the surgically resected adenoma was stained using a mouse monoclonal anti-AIP antibody (1:5000 dilution; NB100-127 B35-2, Novus Biological, Centennial CO, USA), revealing the presence of AIP protein (Fig. 1c) at higher levels than in normal pituitary tissue (Fig. 1d).

Analysis of DNA extracted from the pituitary adenoma using multiplex ligation-dependent probe amplification (MLPA; SALSA P244 probemix, MRC-Holland, The Netherlands) demonstrated the presence of both alleles of the *AIP* gene, consistent with no loss of heterozygosity (LOH).

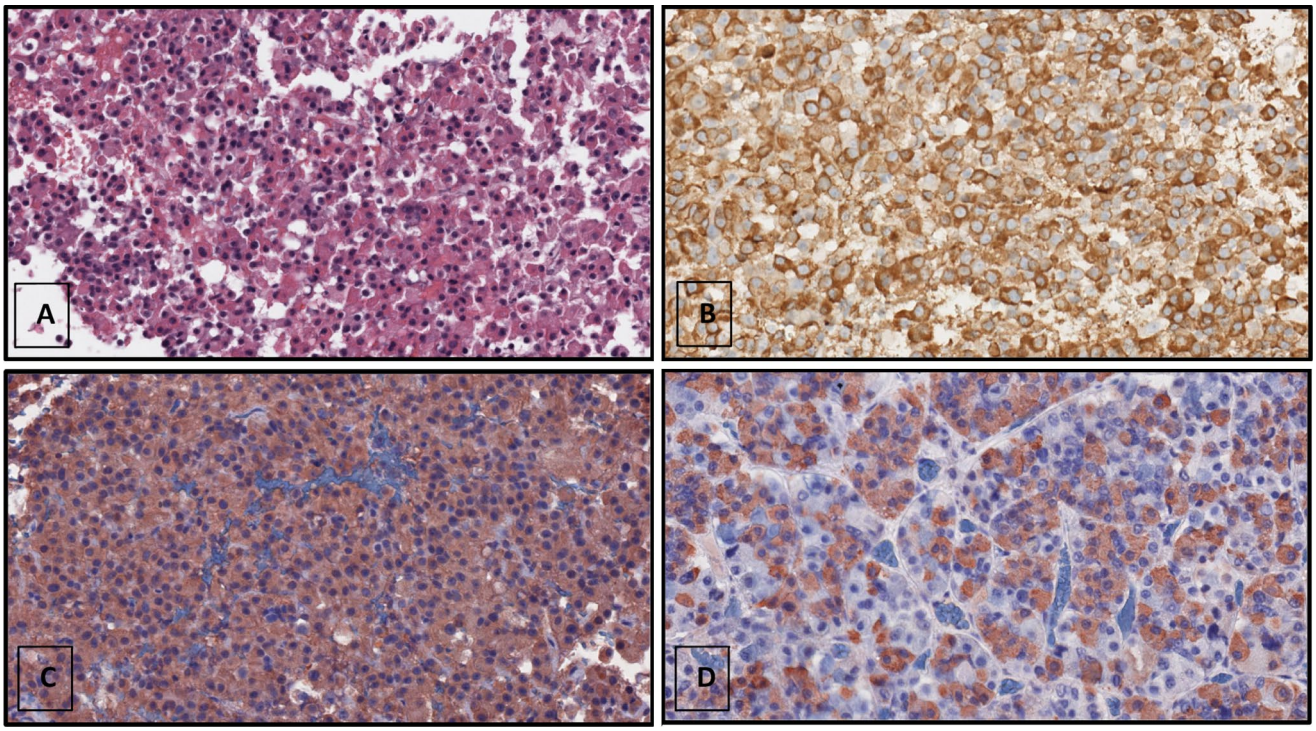

Fig. 1 The pituitary adenoma in the individual with Tatton-Brown-Rahman syndrome stains positive for Growth Hormone and AIP. **a** Pituitary adenoma tumor cells stained with hematoxylin eosin (H&E) (×20). **b** GH Immunohistochemistry showing numerous positive tumor cells (×20). **c** AIP immunostaining showing homogeneous staining, with predominantly positive-staining cells without loss of expression (×20). **d** AIP staining in a normal pituitary gland (×20)

Discussion

TBRS is a recently described genetic syndrome due to heterozygous germline mutations in *DNMT3A*. This condition is inherited in an autosomal dominant manner but most often results from de novo mutations [2, 6]. While physical overgrowth is a common feature of this syndrome, to our knowledge GH secretion has not been studied in these patients. Until now, few endocrinological disorders have been reported in individuals with TBRS and have included precocious puberty, thyroid disorders such as thyroid cysts and hyperthyroidism, and a few cases of polycystic ovarian syndrome, the latter two of which our patient also had [2]. To our knowledge however, pituitary adenomas have not been described in TBRS.

Here we report a patient with TBRS with a GH-secreting macroadenoma diagnosed in adulthood. She was found to carry a heterozygotic *AIP* gene variant of unknown significance (c.25C>T; p.Arg9Trp; rs1057523115). Germline mutations in *AIP* typically lead to early-onset GH-secreting macroadenomas that can present as familial isolated pituitary adenoma syndrome [8]. In the current case, the identified *AIP* change is a variant of unknown significance that is very rare: dbSNP: rs1057523115 (https://www.ncbi.nlm.nih.gov/snp/rs1057523115#variant_details). It leads to a missense change at a poorly conserved residue, and based on in silico analyses, its pathogenicity remains equivocal. Tumoral AIP immunohistochemical staining is not a reliable indicator of the pathogenicity of *AIP* genetic variants, particularly missense changes [9], also because the staining can be altered by pre-surgical somatostatin analog therapy [10]. The main argument against pathogenicity of the *AIP* variant in the current study is the demonstrated lack of LOH. *AIP* acts as a tumor suppressor gene in the pituitary, and germline mutations are accompanied by a somatic "second-hit" to disrupt the normal allele in the tumor DNA leading to loss of heterozygosity [11]. MLPA analysis is widely used for the identification of pathological copy number changes in *AIP* and other genes, and in this case no allelic loss was demonstrated in tumor DNA. Taken together, these results suggest that the pathogenesis of the patient's acromegaly was not due primarily to the *AIP* variant. Indeed, the risk stratification for AIP mutations classifies our patient as low risk (<5%) [12]. It remains possible that against a background of disordered DNA methylation regulation induced by the germline *DNMT3A* mutation, the concomitant *AIP* variant could have contributed to tumorigenesis. For example, an inactivating mutation not detectable by MLPA could be present in *AIP,* or the normal allele could be silenced

by DNA hypermethylation, though this is less likely in the setting of increased AIP staining. It remains possible loss of DNMT3A (and subsequent loss of DNA methylation) could have contributed to abnormally increased AIP expression and this is somehow involved in the mechanism of tumorigenesis. Importantly, *DNMT3A* is disrupted in many tumor types, and in particular overexpression of *DNMT3A* has been reported in aggressive pituitary adenomas [13]. This is however opposite to what we would expect here in the setting of TBRS due to a germ-line inactivating mutation likely resulting in haploinsufficiency.

Acromegaly is a rare disorder, with prevalence ranging between 2.8 and 13.7 cases per 100,000 people, and the annual incidence rates ranging between 0.2 and 1.1 cases per 100,000 people [14]. The median age at diagnosis is in the fifth decade of life. The co-existence of two rare conditions like TBRS and acromegaly could be a chance occurrence. It may be that TBRS can predispose affected individuals to a broader spectrum of tumors than previously thought. Indeed, our patient has had many benign tumors and cystic lesions described above. This seems distinct from other individuals with TBRS reported in the literature, which include two with acute myeloid leukemia (AML) and one with medulloblastoma, as well as other individuals with mostly isolated, benign lesions noted, including an enchondroma, a lipoma, and renal cysts [2]. The heavy disease burden involving many tissues in our patient might reflect her older age as compared with many of the patients described to date in the literature, who mainly come from pediatric populations. Regardless, our findings suggest that long-term follow up of individuals with TBRS may reveal a broader phenotypic spectrum of disease in a wider array of affected tissues as patients age. The presence of GH-secreting adenomas (and possibly other pituitary and distinct tumor types) should be considered in individuals with TBRS with appropriate clinical presentations.

Conclusion

TBRS is a rare Mendelian disorder of the epigenetic (DNA methylation) machinery characterized by several unique clinical features. Our observations expand the clinical phenotype of TBRS to include various tumors that were not previously reported in this disorder with a focus on a pituitary adenoma. The current TBRS literature is mostly limited to pediatric patients in whom no somatotropinomas or other kinds of pituitary adenomas have been reported. However, it remains possible that pituitary adenomas (and possibly other tumors observed in our patient) may be reported in the future as later manifestations of this syndrome.

Author contributions All authors contributed to the study conception, design and approved the final manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Informed consent Written informed consent was obtained from the guardian of the patient included in the study.

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