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Letter to the editor

Tatton-Brown-Rahman syndrome: A new multiple endocrine neoplasia syndrome with intellectual disability?

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ABSTRACT

We describe for the first time the case of a woman presenting with Tatton-Brown-Rahman syndrome (TBRS) and multiple endocrine neoplasia (MEN). She developed primary hyperparathyroidism at age 13, a pituitary cyst at age 14, adrenal tumor at age 21, and metastatic insulinoma at age 34. In addition, she showed intellectual disability, obesity, multiple lipomas, facial dysmorphia, hemihypertrophy and kyphoscoliosis. At age 35, genome analysis revealed a pathogenic de-novo heterozygous germline *DNMT3A* variant, while classic MEN syndromes were ruled out by targeted somatic and germline genetic testing. This case highlights not only the importance of genomic analysis in patients with multiple and atypical conditions, but also the need for a multidisciplinary approach for TBRS patients, including in adulthood, involving endocrinologists to enhance understanding and optimize monitoring of this syndrome.

1. Introduction

First identified in 2014, Tatton-Brown-Rahman syndrome (TBRS, # 615879) is a rare overgrowth syndrome including intellectual disability, primarily caused by a pathogenic de-novo heterozygous germline *DNMT3A* variant [1]. In some rare cases, TBRS is inherited from a parent. *DNMT3A*, located on chromosome 2p23, encodes a DNA methyltransferase that plays a role in establishing parent-of-origin methylation during gametogenesis (de-novo methylation) [2]. Before the description of TBRS, acquired *DNMT3A* mutations were known to be involved in the acute myeloid leukemia and myelodysplastic syndrome [3]). In TBRS, patients exhibit a wide range of clinical manifestations, including mild intellectual disability, behavioral or psychiatric issues, postnatal overgrowth with height and/or head circumference exceeding 2 standard deviations (SDs), and obesity. Facial dysmorphia is also present, with low-set horizontally thick eyebrows, narrow palpebral fissures, coarse features, a round face and enlarged and prominent upper central incisors [4]. Affected individuals also exhibit joint hypermobility, hypotonia, kyphoscoliosis and afebrile seizures.

Here, we present the first case of TBRS exhibiting a phenotype akin to multiple endocrine neoplasia type 1 (MEN1).

2. Case report

2.1. Clinical presentation

This 37-year-old woman had suffered from various endocrine disorders since childhood, alongside obesity and intellectual disability. At birth, she was delivered prematurely at 37 weeks due to gestational hypertension. She presented with macrosomia, weighing 3.57 kg (95th percentile), measuring 51 cm in length (96th percentile), and having a head circumference of 36.5 cm (> 97th percentile). Early in life, she showed signs of hypotonia, experienced a hyperthermic seizure at 15 months, and showed delayed development. She began standing and walking later than average, at 17 and 23 months, respectively. Her language development was also delayed, achieving only a basic vocabulary by the age of 2. Then, she presented behavioral issues, including hyper-aggressiveness. Additionally, she exhibited atypical clinical features, including suspected left-side hemihypertrophy from childhood, due to significant deep lipomas affecting the left arm. She also experienced early childhood obesity and scoliosis, and had distinctive facial features, such as a broad face, thick low-set eyebrows and prominent upper central incisors.

Her medical history was also notable for a non-malignant parathyroid adenoma at the age of 13, which required ongoing cinacalcet therapy due to multiple post-surgical relapses, and for a successfully treated pinealocytoma at the age of 7. Despite clinical signs, acromegaly was not confirmed on pituitary imaging or hormonal tests. A pituitary cyst identified at age 14 suggested a Rathke's cleft cyst. Additionally, a stable infracentimetric adrenal nodule without hypersecretion was detected at age 21. Her condition had recently deteriorated with the discovery of a metastatic insulinoma at the age of 34, after recurrent hypoglycemic episodes for which she was treated with diazoxide. Nuclear imaging (DOTATOC and exendin PET) revealed a tumor in the lower part of the head of the pancreas and possible liver metastases. Surgery removed a 3 cm pancreatic tumor, uncovering 5 neuroendocrine tumors (NETs), 4 of which were insulin-staining positive. These pancreatic NETs were well-differentiated, grade G1, with a low Ki67 of 2%, and

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Table 1
Endocrine or endocrine disease-related lesions reported in TBRS patients.

Variant nomenclature NM_022552.5	Protein nomenclature NP_072046.2	Occurrence	Endocrine or endocrine disease-related lesions	Reference
c.26_27delinsT	p.(Pro9LeufsTer63)	De novo	Early puberty	Tatton-Brown et al., Wellcome Open Res. 2018
c.700_709del	p.(Gly234ArgfsTer79)	Not determined	GH-secreting pituitary macroadenoma, fibrous dysplasia of the maxilla	Hage et al. Pituitary, 2020
c.1320G>A	p.(Trp440Ter)	De novo	Cryptorchidism	Tatton-Brown et al., Wellcome Open Res. 2018
c.1523T>C	p. (Leu508Pro)	De novo	Cryptorchidism	Tatton-Brown et al., Wellcome Open Res. 2018
c.1643T>C	p.(Met548Thr)	De novo	Early puberty	Tatton-Brown et al., Wellcome Open Res. 2018
c.1743G>C	p.(Trp581Cys)	De novo	Cryptorchidism, lipoma, hirsutism	Tatton-Brown et al., Wellcome Open Res. 2018
c.1851+3G>C	p.(?)	De novo	Thyroid cyst	Tatton-Brown et al., Wellcome Open Res. 2018
c.2094G>C	p.(Trp698Cys)	De novo	Menorrhagia	Tatton-Brown et al., Wellcome Open Res. 2018
c.2172C>A	p.(Tyr724Ter)	De novo	Pituitoma, primary hyperparathyroidism, metastatic insulinoma, lipomas, adrenal tumor	Reported here
c.2311C>T	p.(Arg771Ter)	De novo	Advanced bone age	Martin et al., Andes Pediatr. 2022
c.2512A>G	p.(Asn838Asp)	De novo	Testicular atrophy	Tatton-Brown et al., Wellcome Open Res. 2018
c.2644C>T	p.(Arg882Cys)	De novo	Cryptorchidism	Tatton-Brown et al., Wellcome Open Res. 2018
c.2705T>C	p.(Phe902Ser)	De novo	Polycystic ovary syndrome	Tatton-Brown et al., Wellcome Open Res. 2018
Entire gene deletion		De novo	Polycystic ovary syndrome	Tatton-Brown et al., Wellcome Open Res. 2018

varied in size from 0.1 to 1.7 cm in diameter. Unfortunately, celiac lymph node dissection revealed micro-metastasis. However, liver biopsy did not confirm metastasis, but only minor focal macrovacuolar steatosis. Post-surgery, she developed a biliary and pancreatic fistula, hypovolemic shock, portal thrombosis and severe malnutrition. Four months later, recurrence of hypoglycemia suggested relapse of insulinoma, necessitating reintroduction of diazoxide. Subsequent nuclear imaging revealed persistent liver involvement, and a potential new hepatic tumor deposit. Additionally, she developed complications: portal hypertension, gastropathy, thrombocytopenia with hypersplenism, and 16-cm splenomegaly. Presence of multiple pancreatic NETs, early-onset hyperparathyroidism and lipomas was consistent with clinical diagnosis of MEN1 [5], but did not account for the other features: intellectual disability and facial dysmorphia.

2.2. Genetic investigations

Between the age of 20 and 24 years, the patient underwent multiple genetic studies. Karyotype, CGH-array and genetic analyses for fragile X, Prader-Willi and Beckwith-Wiedemann syndromes were negative. Sanger sequencing and multiplex ligation-dependent probe amplification (MLPA) for *MEN1* and *CDC73* were negative. At 35 years, with multiple and early endocrine tumors, next-generation sequencing (NGS) of *MEN1, CDC73, CDKN1B, GCM2, VHL, PRKAR1A*, and *AIP* was performed on blood DNA and revealed no germline punctual or copy number variation [6]. To rule out *MEN1* mosaicism, deep germline NGS and somatic NGS of parathyroid adenoma and hamartoma were performed and revealed no abnormalities. *PIK3CA* sequencing in a lipoma was negative. *PTEN* NGS was also negative.

Finally, trio genome sequencing was performed under the 2025 French genomic medicine initiative (*Plan France Médecine Génomique*). Whole-blood genomic DNA (gDNA) was sequenced according to standard procedures for a PCR-free genome on a NovaSeq6000 instrument (Illumina). Sequencing data were aligned to the GRCh38p13 full assembly using bwa 0.7+. Using several algorithms, GATK4+, Bcftools1.10+, Manta1.6+ and CNVnator0.4+ variants were called and annotated using the variant effect predictor. Detected variants were prioritized using in-house procedures. Further details are available on request on http://www.auragen.fr. Whole genome sequencing revealed a de-novo *DNMT3A* heterozygous pathogenic variant NM_022552.5: c.2172C>A, p.(Tyr724Ter) (GRCH38 chr2:g.25240641G>T).

3. Discussion

We report the first case of TBRS with a clinical presentation similar to MEN syndrome, but where somatic and germline testing ruled this out. TBRS is a recently described syndrome that was initially reported in contexts of intellectual disability. Long-term follow-up and additional case descriptions have revealed the risk of hematological malignancy, which sometimes occurs early in these patients [7]. Cardiovascular diseases (most commonly congenital heart disease and less frequently aortic root dilatation) are also observed and need to be monitored [8–10]. Association with solid tumors remains unclear [4,11,12].

Endocrine disorders in TBRS are not well understood, but a few cases have been described. In 2020, Hage et al. reported a woman with TBRS and a GH-secreting pituitary macroadenoma diagnosed at the age of 34 [12]. Most TBRS cases have been in children, as noted by Hage et al., with few in adults, resulting in limited clinical data for the adult population. Nevertheless, endocrine disorders are frequently reported in TBRS patients (Table 1). For example, cryptorchidism is reported in 20-30% of male patients; more rare, testicular atrophy was reported in 1 patient [10,13]. Early or precocious puberty was reported in 6 patients and menorrhagia in 1 patient [4,13]. Polycystic ovary syndrome was reported in 2 patients [4]. Advanced bone age was reported in 1 patient, lipoma in 1, and thyroid cyst in 1 [4,12,14].

4. Conclusion

Here we report a case of a young woman with TBRS, with multiple complications, including lesions similar to those seen in multiple endocrine neoplasia type 1. In conclusion, we highlight the importance of genomic analysis in patients with multiple and atypical conditions, and the need for a multidisciplinary approach for TBRS patients, including in adulthood, involving endocrinologists to enhance understanding and optimize monitoring of this syndrome.

Disclosure of interest

The authors declare that they have no competing interest.

Ethic statement

This work was based on data produced during normal medical management. The patient and his guardians have given their consent for this scientific publication.

Data availability statement

The whole genome data underlying this article cannot be shared publicly due to privacy reasons. The targeted sequencing data will be shared on reasonable request to the corresponding author.

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Contributions

Conceptualization: PR, AB; funding acquisition: PR, AB; investigation: LLC, TC, AL, SL, GA; methodology: PR, AB; supervision: AB, PR; validation: AFD, BD; writing - original draft: LLC, PR; writing - review & editing: all authors.

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