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REVIEW ARTICLE

Clinical report of Bosma arhinia microphthalmia syndrome with a new variant on SMCHD1 gene. A case report

José Atencia Goñi[a,*], **María Orera Clemente**[b], **Mariano José Del Valle Diéguez**[c], **Laura González Fernández**[a], **Olga González Albarrán**[a]

[a] *Department of Endocrinology and Nutrition, HGU Gregorio Marañón, Madrid, Spain*
[b] *Department of Genetics, HGU Gregorio Marañón, Madrid, Spain*
[c] *Department of Radiology, HGU Gregorio Marañón, Madrid, Spain*

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Abstract The Bosma syndrome (BAMS: Bosma arhinia microphthalmia syndrome) is a condition first described in 1972. Since then, several reviews have published the cases looking for diagnostic criteria and associated genetic alterations. The mutation in the SMCHD1 gene (Structural Maintenance of Chromosomes flexible Hinge Domain containing protein 1) seems to explain a part of the development of the phenotype. Not all cases show the same alterations or meet the classic diagnostic criteria, and few have undergone genetic analysis. We present a case with a new variant in this gene and an update of the literature on this syndrome with the aim of improving the diagnosis and follow-up of these patients.

PALABRAS CLAVE
Trastorno genético;
Hipogonadismo;
Trastornos del crecimiento;
Trastornos del desarrollo sexual

Informe clínico de un caso con síndrome de Bosma Arhinia Microftalmia con una nueva variante en el gen *SMCHD1*. A propósito de un caso

Resumen El síndrome de *Arhinia Microftalmia Syndrome Bosma* (BAMS) es una condición que se describió por primera vez en 1972. Desde entonces, varias revisiones han publicado los casos buscando criterios diagnósticos y alteraciones genéticas asociadas. La mutación en el gen *SMCHD1* (proteína 1 que contiene el dominio flexible de mantenimiento estructural de los cromosomas) parece explicar una parte del desarrollo del fenotipo. No todos los casos muestran las mismas alteraciones o cumplen los criterios diagnósticos clásicos, y pocos han sido sometidos

* Corresponding author.
E-mail address: joseatenciagoni@hotmail.com (J. Atencia Goñi).

a análisis genético. Presentamos un caso con una nueva variante en este gen y una actualización de la literatura sobre este síndrome con el objetivo de mejorar el diagnóstico y el seguimiento de estos pacientes.

Introduction

The first two known cases of Bosma syndrome (BAMS: Bosma arhinia microphthalmia syndrome) were described in 1972 by Gifford et al.,[1] but it was not until 1981 when Bosma et al.[2] published two more cases and gave the syndrome its name. Since then, several authors have shared their cases. In 2016, Brasseur et al.[3] carried out a review with up to 14 possible cases in relation to the syndrome. The different authors who have been incorporating cases into the literature have searched genes related to ocular development, such as PAX6,[4] trying to find a causing mutation. Recently mutations in the SMCHD1 gene (Structural Maintenance of Chromosomes flexible Hinge Domain containing protein 1) have been described as possible causes of the syndrome.

In this article, we describe a case of BAMS seen in our centre and update the current genetic evidence.

Description of the case

The first visit to our department was in 2021. He had been seen first in the genetics consultation where was referred to our endocrinology consultation. This was a man in his 30s with a history of congenital arhinia and left microphthalmia with several reconstructive surgeries in childhood. The patient had his first contact with endocrinology in another centre for hypogonadism study and was diagnosed with hypogonadotropic hypogonadism. Initial treatment consisted of 50 mg of testosterone gel daily. The patient maintained this treatment for one year before discontinuing it on his own due to the appearance of acne.

The initial endocrinology consultation took place over the phone due to the pandemic. During this consultation, the patient reported a previous diagnosis of delayed puberty during their paediatric years. Further inquiry confirmed the presence of hypogonadism, marked by reduced libido, muscle strength, and diminished secondary sexual characteristics. The blood test results (refer to Table 1) indicated hormonal values consistent with hypogonadotropic hypogonadism, along with low growth hormone (GH) levels. Treatment was started again with 50 mg daily of testosterone gel and a new appointment was requested including a pituitary magnetic resonance, bone densitometry and another blood test.

Management

At the three months review consultation he reported a clear improvement in symptoms with recovery of sexual function and a better muscle strength and general condition. The analytical results (Table 1) showed higher testosterone values with normalization of GH and the appearance of high IGF-1 values not previously seen. Bone densitometry showed a *Z*-score of −1 in the femoral neck and −1.8 in the lumbar spine compatibles with osteopenia. The pituitary resonance report indicated:

- Pituitary stalk and parenchyma atrophy.
- Right microphthalmia.
- Atrophy of the right optic nerve and left optic tract.
- Atresia of the nasal cavities secondary to a fusion of the palatine bone and the maxillary palatine process with the sphenoid and ethmoid bones.
- Absence of frontal and sphenoid pneumatization.
- Bilateral dacryocystoceles.

In Fig. 1 we can see the pituitary magnetic resonance of the patient with three perspectives.

Regarding the genetic study, the family tree did not show direct relatives with similar characteristics. Only one nephew had a lip and palate cleft. A Next Generation Sequencing (NGS) panel was requested, which included the genes associated with features of the patient. The SMCHD1 gene was sequenced, revealing the mutation c.400G>T, p.(Ala134Ser) considered likely pathogenic. This confirms the diagnosis of BAMS syndrome (OMIM: 603457). Subsequently, the same variant was studied in her sister, identifying that she is not a carrier.

The analytical results of the third visit are also shown in Table 1. Maintaining the dose of 50 mg daily of testosterone gel, the values of testosterone in the blood normalized. The patient did not report previous errors in the administration of testosterone or new symptoms. The improvement of muscle strength and sexual function was maintained. At the physical examination there were no suggestive changes of acromegaly. The treatment of hypogonadism was maintained the same and vitamin D was added due to deficiency detected in blood analysis.

He is currently undergoing check-ups in an endocrinology clinic to control hypogonadism as well as the rest of associated comorbidities.

Areas of uncertainty

Brasseur et al.[3] propose four clinical characteristics to define the syndrome and narrow down the existing cases:

- Arhinia.
- Maxillary hypoplasia in half face (*hypoplastic maxilla*).

Table 1 Blood test results on the first, second and third visit.

Item (unit)	First visit	Second visit	Third visit	Reference values
ACTH (ng/l)		12.6		5–60
Cortisol (μg/dl)		8.1	12.3	5–25
FSH (UI/l)		<0.1	<0.1	1–12
LH (UI/l)	<0.1	<0.1	<0.1	0.6–12
GH (μg/l)	<0.05	1.29	0.41	0.1–5
IGF-1		383	322	113–250
IGF-1 age SD			3.45	−2 to +2
Prolactin (UI/l)		10.6	10.1	3.5–19.4
TSH (mUI/l)	1.09	1.46	2.68	0.35–4.94
T4L (ng/dl)		0.9	0.8	0.7–1.48
Testosterone (μg/l)	0.2	7.2	6.1	2.4–8.7
Free testosterone (ng/l)	1.08	22.5	22.94	7–40
SHBG (nmol/l)		40		13.5–71.4
Plasma Osm (mOsm/kg)		301	289	280–300
Urine Osm (mOsm/kg)		1023	192	350–700
Na (mmol/l)		150	143	135–145
K (mmol/l)		5.7	5.5	3.5–5.2
Creatinine (mg/dl)		1.14	1.03	0.7–1.2
GF CKD-EPI (ml/min/1.73 m^2)		84	90	60–100

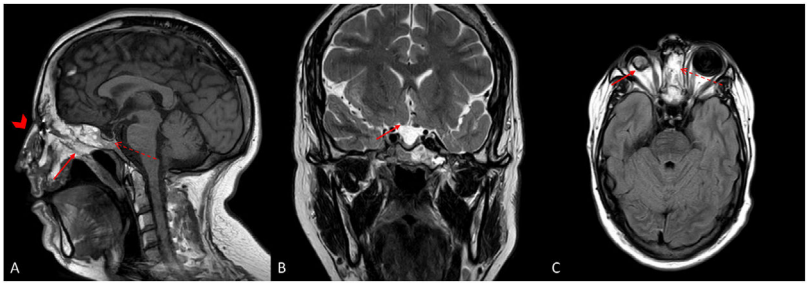

Figure 1 (A) Sagittal T1 weighted sequence showing absent nasal cavity and high arched palate due to confluence of maxilla, sphenoid and ethmoid bones (red arrow). Hypophyseal atrophy (dashed arrow) and surgical nasal reconstruction (arrowhead) are also noted. (B) Coronal T2 sequence reveals markedly atrophic right optic nerve (red arrow). (C) Axial FLAIR demonstrating right microphthalmia (red arrow) and absent ethmoid neumatization (dashed arrow).

- Hypogonadotropic hypogonadism in men.
- Normal intellectual development.

Our case meets these four criteria in addition to showing other alterations also described in the literature, such as microphthalmia or nasolacrimal duct involvement. Other alterations can be seen at the pituitary gland together with hypogonadism and some abnormal GH levels that in our case are pending confirmation. There are no other pituitary axes deficits.

From the genetics point of view, the protein encoded by the SMCHD1 gene is a chromatin modifier with repressive epigenetic activity that is involved in various processes:

- Inactivation of the X chromosome, from the hypermethylation of regions of this chromosome rich in C and G (CPG islands).
- Hypermethylation of the D4Z4 region, close to the DUX4 gene, which remains inactive in most cells. SMCHD1 mutations can reactivate this gene, giving rise to facioscapulohumeral dystrophy type 2.
- Development of the nose, eyes and midline structures. Various mutations with amino acid change (missense) in the C-terminal region associated with BAMS have been described.[5]

The exact mechanism through which pathogenic variants of SMCHD1 disrupt facial development remains unclear.[6] It seems that the ATPase domain might be implicated in the development of the phenotype. All BAMS-associated variants identified so far have a missense variant located at the C-terminal of the ATPase domain, specifically in a region believed to interact with chromatin or recruit other interacting elements.[7]

In this context, Gurzau et al.[8] proposed a theory suggesting that the functioning mechanism of SMCHD1 relies on conformational changes facilitated by a hinge zone, resulting in a V-shaped structure. These changes necessitate the completion of all components within the ATPase domain. Once the protein is appropriately configured, it is poised to

Table 2 Summary of published cases related to BAMS including known genetic mutations. Data updated from the publication of Brasseur et al.[3]

Item	Patients																	
	Bosma et al. [1981] Patient M[2]	Bosma et al. [1981] Patient D[2]	Graham and Lee [2006] Patient 1[9]	Graham and Lee [2006] Patient 2[9]	Shino et al. [2005][10]	Hou et al. [2004]; Sato et al. [2007] Patient A[11]	Sato et al. [2007] Patient B[11]	Sato et al. [2007]; Muhlbauer et al. [1993] Patient C[11]	Sato et al. [2007]; Olsen et al. [2001] Patient D[11]	Sato et al. [2007]; Sakai et al. [1989] Patient E[11]	Tryggstad et al. [2013][12]	Courtney et al. [2014][13]	Becerra-Solano et al. [2015][14]	Brasseur et al. [2016][3]	Cong et al. [2023][15]	Bargiela et al. [2023] Patient I[16]	Bargiela et al. [2023] Patient II[16]	Our patient
Sex	Male	Male	Male	Male	Male	Female	Male	Female	Female	Male	Male	Female	Male	Male	Female	Female	Female	Male
Arhinia	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hypoplasia maxilar	+	+	+	+	–	+	+	+	+	–	+	–	+	+	+	+	+	+
Micro/ anophthalmia	+	–	+	+	–	+	+	–	+	–	–	+	+	+	+	–	–	+
Hypogonadism hypogo-nadotropic	+	+	+	–	–	–	+	–	–	–	–	–	+	+	?	–	–	+
Normal cognition	+	+	+	+	+	Develop-mental delay	Autism	+	+	+	+	Unknown	+	+	+	+	+	+
Cryptorchidism	+	+	+	–	–	–	–	–	–	–	+	–	+	+	–	–	–	–
Anosmia	+	+	+	–	+	–	–	–	–	–	+	–	–	+	+	+	+	+
Genetic testing	–	–	–	–	–	+	+	+	+	+	+	–	+	+	–	+	+	+
SMCHD1 tested	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	+	+
Gen mutation	–	–	–	–	–	Del 9q11-q13	–	–	–	–	–	–	–	Variant PCSK2	–	SMCHD1	SMCHD1	SMCHD1

interact with the promoter and enhancer regions of genes, exhibiting the ability to induce epigenetic modifications and influence gene expression.[17]

Knowing these data, Gordon et al.[18] sequenced the SMCHD1 gene in 14 patients with a syndrome compatible with BAMS, finding 6 cases with previously described missense mutations in the hinge region along with 7 other unknown missense mutations in the same region. Fifty percent of the mutations are found in exon 3 and the rest between exons 5–13. Seeking to correlate these results with arhinia, they researched in mice finding that SMCHD1 is overexpressed during early nasal development in the olfactory epithelium. Hence, it seems, therefore, that the previously described mutations specifically affect this stage of development, giving rise to the phenotype of the syndrome.

Facioscapulohumeral muscular dystrophy type 2 (FSHD2) and BAMS have in common the involvement of the SMCHD1 gene.[19] However, patients with alterations in this gene and BAMS typically exhibit a gain of function, while in FSHD2, there is usually a loss of it.[20] As highlighted by Mul et al.,[21] mutations in SMCHD1 alone are deemed insufficient to account for the entirety of these two disorders.

From an endocrinological perspective, the abnormalities observed in these patients may be associated with inherited defects in the early olfactory epithelial cells. These cells migrate to form the pituitary gland, potentially leading to hypogonadotropic hypogonadism in adulthood, along with other complications in the sexual sphere, such as cryptorchidism or delayed puberty.[12] Other complications such as growth retardation remain to be clarified, but we do not have a genetic analysis as exhaustive as the one described to confirm whether these patients meet these genetic alterations. Our case presents elevated IGF-1 values with normal GH and normal growth. As the patient did not exhibit IGF-1 values exceeding 1.3 points above the upper limit of normal and did not display symptoms indicative of acromegaly, we deemed it unnecessary to pursue additional studies, such as GH testing following oral glucose overload. Moreover, there are no reported instances in previous literature of BAMS being associated with acromegaly. Genetic alterations of SOX2[19] produce microphthalmia and hypogonadism[22] but not a complete BAMS and in these cases the tendency is to the deficiency of the growth hormone. More information is needed to go further into this issue.

In the case of our patient, a missense variant is identified in exon 3, which corresponds to the hinge region. This variant had not been previously described. This finding correlates with Gurzau et al.[8] and contributes to amplify what we know about these mutations.

To update the cases presented by Brasseur et al.[3] we did a second review searching for SMCHD1 mutations in these articles. Table 2 summarizes the updated collected data including two articles published in 2023. We can see how not all cases meet the four criteria proposed by themselves, with arhinia and maxillary hypoplasia being the most frequent. There are patients who did not present normal intellectual development and the prevalence of male hypogonadism is lower than expected (7/11). The family described by Bargiela et al.[16] has a new variant of SMCHD1 (heterozygous missense p.E473V variant (c.1418A>T) in exon 11) that conditions congenital arhinia in two subjects and anosmia in another. The BAMS case from Vietnam did not perform genetic sequencing. In our opinion, a genetic study in this direction would provide important information and could change the diagnosis of BAMS for the patients not meeting the Brasseur criteria if they are validated. The fourteen cases studied in Ref. 18 are different from those published in Table 1.

Guidelines

From a practical point of view, there are no consensus guidelines for the treatment and follow-up of this syndrome. Congenital arhinia should be the first sight to rule out its diagnosis. An assessment by the specialist will be necessary to determine the needs for reconstructive surgery. Of course, it is advisable to perform a genetic test to confirm the presence of any of the known or new variables. From a sexual point of view, it is necessary to explore these patients and monitor complications such as cryptorchidism. Likewise, it is necessary to monitor hypogonadism and ensure complete sexual development and adequate replacement in adulthood. It may be indicated to perform a screening of other pituitary deficits. Other recommendations could be to monitor the development of osteoporosis in adulthood and perform an ECG to rule out defects described as the blurring of the sinotubular crest or the persistent ductus arteriosus.

Conclusions and recommendations

BAM syndrome is a very rare pathology, caused by mutations of the SMCHD1 gene, which generally appear de novo.

We present a new case that meets all the clinical diagnosis criteria for this syndrome in which a novo missense-type variant has been identified. It is highly probable that the identified variant is the cause of the patient's phenotype. More data is required to validate the clinical diagnosis criteria and to stablish the genetic test criteria.

All this information shows the need to deepen the genetic study of these patients. New cases should be tested for mutations in the SMCHD1 gene and, if possible, search for these mutations in the known patients.

Authors' contributions

Each author acknowledges that he/she has contributed in a substantial way to the work described in the manuscript and its preparation.

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Conflicts of interest

All authors declare that they have no conflicts of interest.

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