CASE REPORT

Pituitary hypoplasia and growth hormone deficiency in a patient with Coffin-Siris syndrome and severe short stature: case report and literature review

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ABSTRACT

Coffin-Siris syndrome (CSS) is a rare genetic disorder caused by the haploinsufficiency of one of the various genes that are part of the Brahma/BRG1-associated factor (BAF) complex. The BAF complex is one of the chromatin remodeling complexes, involved in embryonic and neural development, and various gene mutations are associated with cognitive impairment. CSS has a highly variable genotype and phenotype expression, thus lacking standardized criteria for diagnosis. It is generally accepted to associate 5th digit/nail hypoplasia, intellectual disability (ID)/developmental delay and specific coarse facial features. CSS patients usually display miscellaneous cardiac, genitourinary and central nervous system (CNS) anomalies. Many patients also associate intrauterine growth restriction, failure to thrive and short stature, with several cases demonstrating growth hormone deficiency (GHD). We report the case of a 4-year-old girl with severe short stature (-3.2 standard deviations) due to pituitary hypoplasia and GHD that associated hypoplastic distal phalanx of the 5th digit in the hands and feet, severe ID, coarse facial features (bushy eyebrows, bulbous nose, flat nasal bridge, dental anomalies, thick lips, dental anomalies, bilateral epicanthal fold) and CNS anomalies (agenesis of the corpus callosum and bilateral hippocampal atrophy), thus meeting clinical criteria for the diagnosis of CSS. Karyotype was 46,XX. The patient was started on GH replacement therapy, with favorable outcomes. Current practical knowledge regarding CSS diagnosis and management from the endocrinological point of view is also reviewed.

KEYWORDS: Coffin-Siris syndrome; BAF remodeling complex; short stature; GH deficiency; CNS malformations

INTRODUCTION

Coffin-Siris syndrome (CSS) is a rare genetic multisystemic disease caused by heterozygous mutations in a large panel of genes that are part of the Brahma/BRG1-associated factor (BAF) complex [1]. The BAF complex plays an essential role in chromatin remodeling, and pathogenic variants in several of its components, including *ARID*, *SMARC* and *SOX* family genes, have been associated with CSS [2]. Although other BAFopathies have also been described, CSS is the most well-known; it is also acknowledged as the "fifth digit syndrome", as it was initially described by Coffin and Siris [3] in three unrelated probands that associated severe mental disability and 5th finger/nail hypoplasia. The clinical phenotype is highly variable, with many features which are nonspecific and can also be encountered in other genetic disorders, thus rendering the diagnosis a real challenge in clinical practice. Fleck et al. [4] proposed minimal criteria for the diagnosis of CSS, which is classically described as the association of typical coarse facial features, cognitive disability and developmental delay, 5th finger/nail hypoplasia and hypertrichosis/hirsutism. However, the clinical spectrum of manifestations is very wide, with various degrees of cognitive delay and miscellaneous cardiac, gastrointestinal, genitourinary and central nervous system (CNS) malformations [5]. Around 300 subjects with known mutations were enrolled in the CSS/BAF complex registry in 2021 [1,6].

Part of the constitutional features, short stature is common in CSS (66% in the cohort described by Schrier et al. [7]). While approximately half of the patients are reported to have intrauterine growth restriction at birth, most of them are further on presented as "failure to thrive" [7]. Baban et al. [8] reported in 2008 a case of pituitary hypoplasia, with growth hormone deficiency (GHD).

We report the case of a 4-year-old female patient with intellectual disability (ID), severe short stature due to GHD and severe CNS malformations, in which genetic examination revealed CSS. The manuscript also highlights the importance of genetic evaluation in short stature, the

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correlation genotype-phenotype and differential diagnosis of CSS, as well as the associated endocrinological abnormalities.

CASE PRESENTATION

We present the case of a 4-year-old girl with personal history of iron deficiency anemia, vitamin D deficiency rickets, ID and hyperkinetic disorder, admitted to the Pediatric Endocrinology Department for the investigation of severe short stature. Family history was unavailable, as she was in foster care. On clinical examination, her height was 91 cm (-3.2 standard deviations – SD, according to national nomograms [9], $<3^{rd}$ percentile according to the World Health Organization) [10], she was underweight (body mass index=12.1 kg/m2, $<1^{st}$ percentile) and had microcephaly (head circumference= 43 cm, $<3^{rd}$ percentile), cognitive disability and developmental delay (predominantly in the linguistic area). She had coarse facial features: bushy eyebrows, bulbous nose, flat nasal bridge, dental anomalies, thick lips, dental anomalies, bilateral epicanthal fold. She associated pectus excavatum and bilateral hypoplastic nails of the 5^{th} finger and toe. Other anomalies included scoliosis and pilonidal sinus (Figure 1).

Hormonal profile showed normal thyroid and adrenal function, a low basal growth hormone concentration and insulin growth factor-1 (IGF-1) levels towards the lower limit of normal (Table 1). Since basal GH may also be encountered in normal children (due to its neural control with intermittent release) [11], further dynamic testing for GHD was performed, according to the national protocol. Arginine (inhibits somatostatin release from the hypothalamus) and glucagon (generates fluctuation in blood glucose) stimulate GH secretion and are frequently used for GHD testing, with minimal side effects (nausea, vomiting, abdominal pain in both, late hypoglycemia for glucagon) [12,13]. In our patient, GH concentrations failed to increase above the cut-off of 7 ng/ml at arginine and glucagon stimulation tests, respectively. No side effects occurred.

Blood chemistry was otherwise normal, as well as vitamin D levels (Table 1). Screening for celiac disease was negative. Bone-age was delayed by 2 years compared to the chronological age and the hand and foot X-rays confirmed hypoplastic distal phalanx of the 5^{th} digit in the hands and feet (Figure 2). Therefore, GHD was confirmed, and brain MRI was performed, revealing agenesis of the corpus callosum, bilateral hippocampal atrophy and pituitary hypoplasia (Figure 3). Echocardiography and abdominal ultrasound were normal. Ophthalmological examination revealed convergent strabismus in the left eye. Audiogram was normal. Karyotype was 46,XX.

Taking into account the clinical and radiological findings, the patient met the clinical criteria proposed in 2012 by Schrier et al. [7], and thus genetic examination established the diagnosis of CSS on the basis of: ID associated with hypoplastic 5^{th} finger/nail, coarse facial features and

Table 1. Results of the hormonal assessment.

Parameter	Value	Normal range
TSH (uUI/ml)	2.4	0.33-6.3
FT4 (ng/dl)	1.02	0.89-1.76
Cortisol (8 AM) (ug/dl)	18	5-25
GH (basal) (ng/ml)	0.7	0-8
IGF1 (ng/ml)	50.4	49-289
25(OH)D3	31	>30

TSH= thyroid-stimulating hormone, FT4= free T4, GH= growth hormone, IGF1= insulin-like growth factor 1.

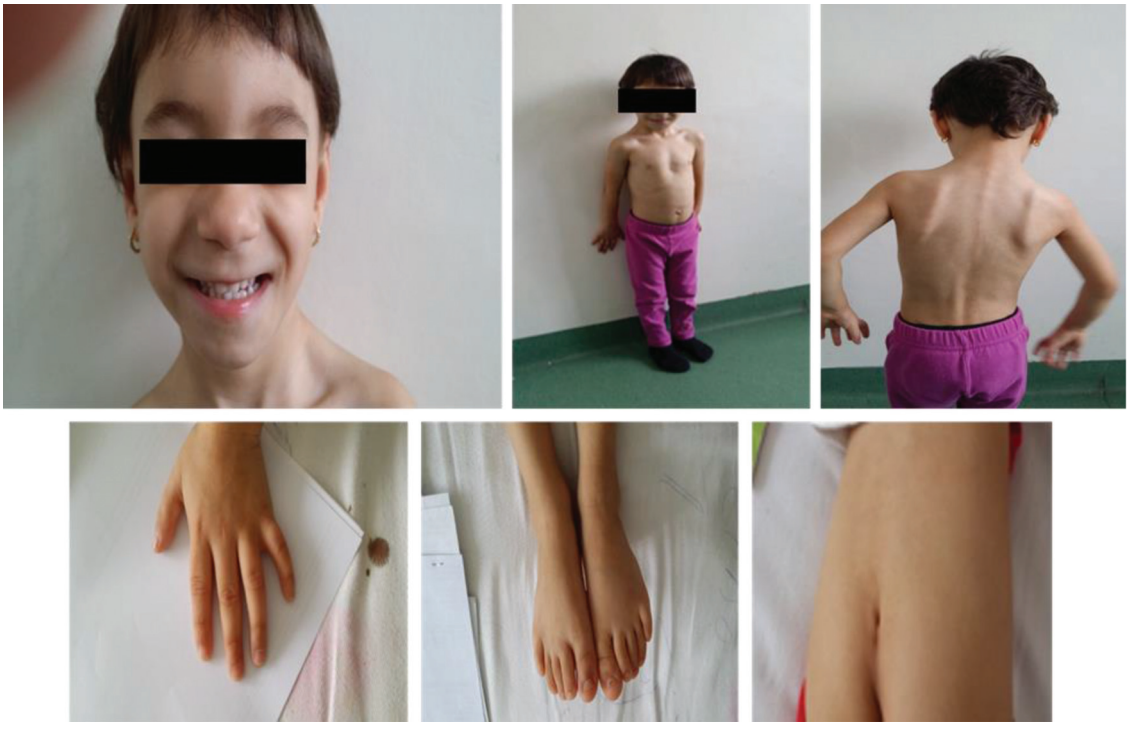

Fig. 1. Clinical examination of the patient revealing short stature, bushy eyebrows, bulbous nose, flat nasal dental anomalies, thick lips, pectus excavatum, bilateral hypoplastic nails of the 5^{th} finger and toe, scoliosis and pilonidal sinus.

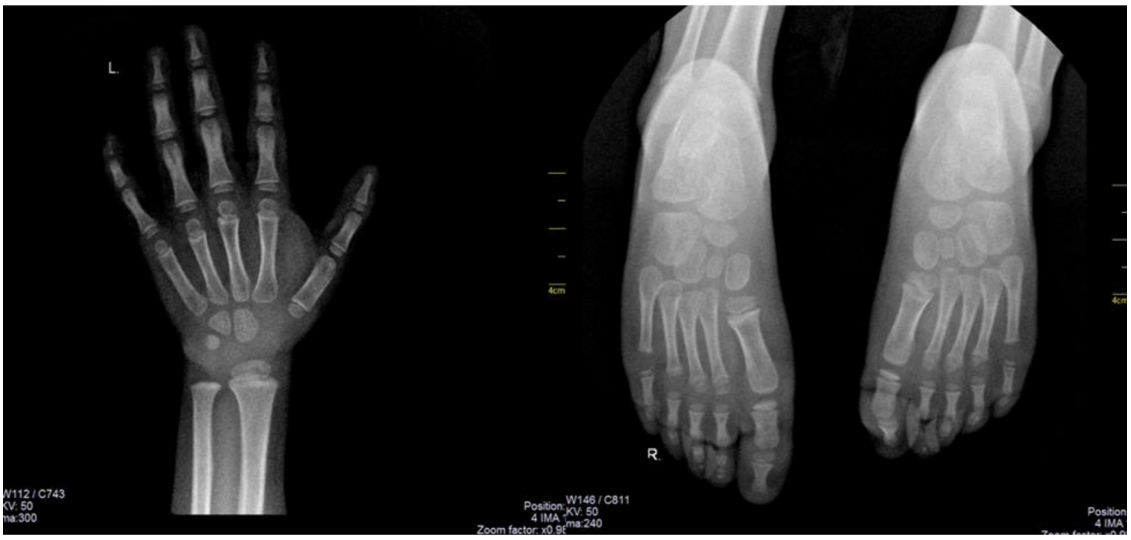

Fig. 2. X-rays of the hands and feet showing delayed bone age and hypoplastic distal phalanx of the 5th digit in the hands and feet.

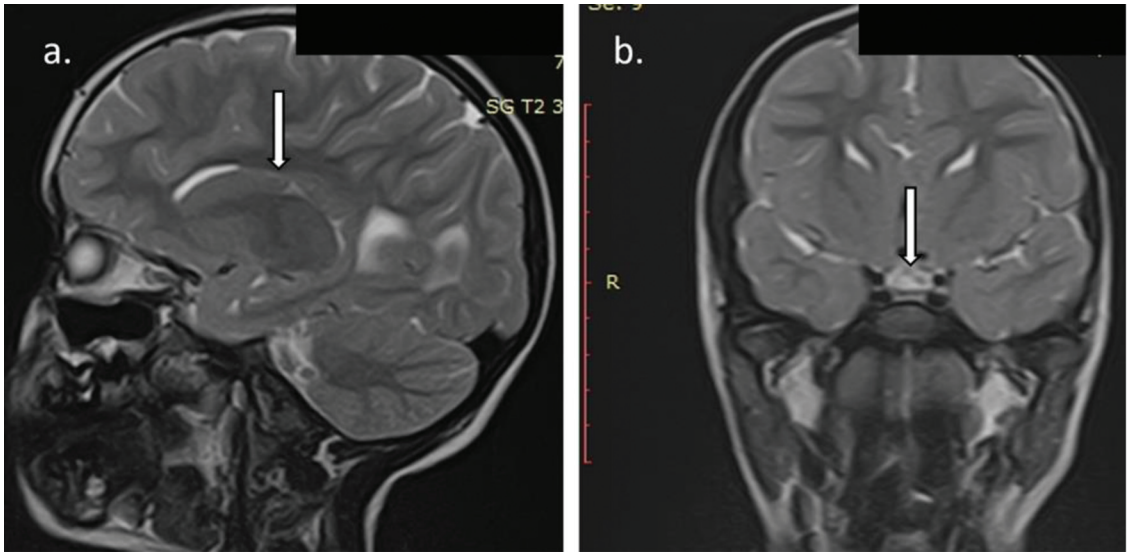

Fig. 3. Brain MRI revealing agenesis of the corpus callosum (a.) and pituitary hypoplasia (b.).

systemic ectodermal (dental anomalies), constitutional (microcephaly, short stature) and organ-related (brain malformations) features. Molecular testing for gene defects associated with CSS was, unfortunately, not available.

The child was started on recombinant human GH (rhGH) replacement therapy 0.035 mg/kg/day, with excellent response: she gained 12 cm in height in the first 12 months of treatment, entering the normal growth curve for age (103 cm, -2SD according to the national nomograms [9]). She continued pediatric neuropsychiatric and endocrinological monitoring.

DISCUSSION

Short stature in children is a common referral reason in pediatric endocrinology, and standard investigations comprise pituitary function along with GHD testing, thyroid function assessment and laboratory work-up for organic causes of growth failure (e.g. renal, hepatic, gastrointestinal disorders, celiac disease, inflammatory disorders) [14,15]. Genetic evaluation for short stature usually comprises evaluation for Turner syndrome in girls, *SHOX* gene deficits or Silver-Russel syndrome. However, the need for genetic evaluation of various monogenic causes of short stature is undervalued, especially in the absence of definitive criteria for selecting patients who would truly benefit from genetic examination and testing [14-16]. Dauber et al. [16] proposed that children exhibiting a height below -3 SD or a height < -2.5 SD with at least one more additional feature, such as the presence of microcephaly, ID, severe GHD and/or multiple pituitary hormone deficiency, additional dysmorphic features or malformations, GH insensitivity, evidence of skeletal dysplasia, being born

short-for-gestational-age (SGA) without catch-up growth or having a single parent with severe short stature, should be genetically evaluated, as they have a high degree of suspicion for underlying genetic mutations explaining their short stature. This would not only provide an explanation for their family but would also help diagnose other congenital anomalies that could be present [16].

Chromatin remodeling via nucleosome alteration and repositioning underlies gene transcriptional regulation. The BAF complex is one of the ATP-dependent chromatin remodeling complexes, involved in embryonic and neural development, via the regulation of neuron-specific gene expression up to adulthood. Recent genome wide-association studies led to the discovery of several neuron-specific BAF subunit gene mutations, mainly associated with neurodevelopmental disorders, among which the most well-known is CSS [17]. Up to the writing of this manuscript, identified BAF subunit mutations associated with CSS include *ARID1A*, *ARID1B*, *ARID2*, *SMARCA4*, *SMARCB1*, *SMARCE1*, *SMARCC2*, *DPF2*, *SOX4* and *SOX11* [1,6,18] (Table 2). Most cases appear *de novo* and are inherited in an autosomal dominant manner [5]. Two thirds of the mutations in CSS are caused by *ARID1B* mutations. *ARID1B* haploinsufficiency is associated with syndromic short stature, thus explaining growth retardation in CSS, while *de novo* missense mutations are associated with idiopathic short stature, without developmental delay [1,19]. The clinical phenotype associated with reduced AT-rich interactive domain-containing protein 1B (ARID1B) levels in CSS is highly variable, probably due to the expression variability of other subunits of the BAF complex. Nevertheless, *ARID1B* is likely to play an important role in brain development, as ID is consistently reported [20]. Large-scale exome sequencing studies found *ARID1B* variants in unspecified cohorts with ID [21,22]. Recent research draws the attention towards the presence of only minor differences between *ARID1B* pathogenic variants causing CSS and *ARID1B* mutations causing ID, thus recommending similar management in both conditions [23].

Table 2. Various BAF mutations and associated distinct phenotype traits in CSS.

BAF subunit mutation
• *ARID1A* Important delay in walking and crawling
• *ARID1B* 2/3 of CSS cases ID consistently reported Prominent hypertrichosis
• *ARID2* Shorter birth length
• *SMARCA4* Frequent anatomic anomalies Milder ID
• *SMARCB1* Severe CSS phenotype, important speech delay, frequent kidney malformations
• *SMARCE1* Frequent kidney malformations Scoliosis
• *SMARCC2* Cardiac abnormalities
Other variants reported:
• *DPF2* Possible craniosynostosis
• *SOX4* Mild facial dysmorphism
• *SOX 11* Syndactyly of toes 2-3 Ocular anomalies

CSS= Coffin-Siris syndrome, ID= intellectual disability.

A recent large genotype-phenotype correlation revealed similar phenotypes across all genetic variants in CSS: the most common phenotypes reported were the classical fifth digit/nail hypoplasia (41%), sparse scalp hair (47%), hypertrichosis (52%) and hypotonia (43%). However, distinct phenotype traits may be encountered with different genetic variants (Table 2) [1,24-26].

The most noticeable differential diagnosis to consider is Nicolaides-Baraitser syndrome, also part of the BAFopathies, characterized by mutations in the *SMARCA2* gene. It overlaps with CSS with regards to the presence of characteristic coarse facial features, sparse scalp hair and ID, but usually the 5th digit nail/distal phalanx hypoplasia/aplasia is absent, with other digital anomalies being present (prominence of interphalangeal joints or of distal phalanges) [5].

Fetal alcohol syndrome should be considered due to the association of hypoplastic nails, growth restriction and multiple congenital organ anomalies, especially concerning the CNS. However, the typical facial features are clearly distinct: short palpebral fissure, smooth philtrum and thin upper vermillion [27].

Other overlapping syndromes include (1) Brachymorphism-Onychodysplasia-Dysphalangism (BOD) syndrome which shares the short 5th finger, dysplastic nails, wide mouth, broad nose, but typically milder ID, (2) DOOR syndrome (deafness, onychodystrophy, osteodystrophy and mental "retardation") which is distinguished by the association of osteodystrophy and profound hearing loss), (3) Cornelia de Lange syndrome which may associate 5th finger hypoplasia, ID and multiple cardiac, gastrointestinal and genitourinary malformations, but has distinctive craniofacial features (arched eyebrows, upturned nose, small teeth and microcephaly), (4) Mabry syndrome which overlaps CSS due to the presence of coarse facial features, hypoplastic 5th digit and ID but presents itself with very high levels of serum alkaline phosphatase and (5) 4q21 deletion syndrome presenting with curbed 5th digit nail and ID, but with characteristic facial appearance (broad forehead, widely spaced eyes and frontal bossing) [1,7].

In the absence of standardized criteria, Schrier et al. [7] proposed an algorithm that might help clinicians to evaluate the likelihood of CSS in a suspected individual. Thus, ID and/or developmental delay together with 5th digit/nail hypoplasia must be present in order to further consider the diagnosis of CSS. Afterwards, at least one feature in each of the following three categories of anomalies must be present: (1) ectodermal (hirsutism/hypertrichosis or sparse scalp hair or dental anomalies), (2) constitutional (microcephaly, or intrauterine growth restriction or failure to thrive or short stature or frequent infections) and (3) organ-related (cardiac or gastrointestinal or renal or brain/cranial malformations, vision problems or hearing loss). Further on, the combination of specific facial features at the level of eyebrows and lips – both thick in type A CSS or thin in type B CSS- must be present. Differential diagnoses must be made with the above-mentioned syndromes [7]. This algorithm is highly valuable for clinicians in the absence of standardized criteria for CSS diagnosis, especially if genetic testing is not possible.

Our patient met all the criteria in the algorithm of Schrier et al. [7] (ID and hypoplastic 5th finger and nail, ectodermal-dental anomalies, constitutional- microcephaly and short stature, organ-related- brain malformations and vision problems) with facial features matching type A CSS. Genetic testing for *ARID1B* was, unfortunately, not possible. At this time point, the diagnosis of CSS is mainly clinical, due to the high variability of genotype and phenotype expression [28]. However, as genetic knowledge is growing, one would expect genetic testing to fit the criteria for CSS diagnosis in the future.

Endocrinological evaluation and growth monitorization is recommended in CSS caused by *ARID1B* gene mutation. In a recent cohort, 7 out of 51 patients were diagnosed with GH deficiency, similar to our patient [23]. Also, around 30% of the patients were appreciated to have short stature. Thus, GH deficiency may be under recognized in *ARID1B* genetic variant, while GH therapy is reported in a limited number of CSS cases [23,29]. Recently, growth charts for individuals with CSS gave been published [29].

CONCLUSION

The association between ID/developmental delay and 5th finger/nail hypoplasia should raise the suspicion of CSS. Growth should be assessed and monitored if CSS is confirmed. CNS anomalies, including pituitary hypoplasia, should be assessed. If GHD is confirmed, GH therapy should be started.

Conflict of interest

The authors declare that they have no competing interests.

Informed consent

Written informed consent was obtained from the caregivers for the publication of the medical data and accompanying images.

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