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Severe Multi-Organ Involvement in A Preterm Baby Affected by SMARCB1 de novo Mutation: A Case Report

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ABSTRACT

Coffin Siris Syndrome (CSS) is a rare neurological syndrome, which can be associated with other malformations, such as cardiac, gastrointestinal, genitourinary, and sensory abnormalities. It is most frequently caused by heterozygous de novo mutations in *ARID1A*, *ARID1B*, *ARID2*, *SMARCA4*, *SMARCB1*, *SMARCE1*, *SOX11*, and *SOX4*. Mutations in *SMARCB1* are associated with a worse neurological phenotype and kidney abnormalities and represent 7-12% of all CSS cases.

We report the case of a late preterm baby with severe multi-organ compromise since birth: agenesia of corpus callosum, developmental delay, complete dysphagia, trachea-bronchomalacia which required mechanical ventilation, bilateral hydronephrosis, neurosensorial hypoacusia, frequent infections. When two months old, he was diagnosed with a de novo *SMARCB1* mutation. The patient was hospitalized for eight months due to multiple complications.

Keywords: Coffins Siris Syndrome, SMARCB1; Agenesia corpus callosum; Developmental Delay; Neonatal Intensive Care Unit

INTRODUCTION

Coffin Siris Syndrome (CSS, MIM#135900) is a multi-system rare genetic disorder; its prevalence has been estimated in less than 1:100000.[1] It is most frequently caused by heterozygous de novo mutations in *ARID1A*, *ARID1B*, *ARID2*, *SMARCA4*, *SMARCB1*, *SMARCE1*, *SOX11*, and *SOX4*.[2,3] Most of these genes encode components of the BAF complex (BRG1-associated factor), which is a chromatin-remodeling complex required for normal organ development.[4-6] Its main clinical characteristics are facial dysmorphisms, digit and integumentary abnormalities, developmental delay of varying degrees, which can be associated with other organ malformations, including cardiac, gastrointestinal, genitourinary, sensory and central nervous systems.[2,3,7]

About 250 cases have been reported in the literature, confirmed by genetic analysis. Prevalence and incidence are unknown, but the disease is probably underestimated.

We describe the case of a late preterm baby with severe multi-organ involvement; at two months of age a de novo mutation in SMARCB1 was identified through Whole Exome Sequencing and the diagnosis of Coffin Siris Syndrome was made. He was hospitalized for eight months due to many serious complications and evolution of the disease.

CASE REPORT

We report the case of a patient who was born at 34 weeks and 6 days of gestation from spontaneous vaginal delivery; on prenatal ultrasound (27+6 weeks of gestation) multiple brain (corpus callosum agenesia, ventricle dilation) and kidney (bilateral hydronephrosis) malformations were identified. Deflection of growth occurred in the last trimester (from 50th percentile to 3rd percentile). No further testing was performed according to parents' will.

His parents are from North Africa, non-consanguineous. The mother is affected by uterine malformation (bicornuate uterus) and underwent surgical removal of one accessory uterine horn and the left ovary. They have a 2 year old son apparently in good condition. Family history was negative for hereditary disease.

At birth the patient reported required prolonged resuscitation with difficult intubation. He was admitted to the Neonatal Intensive Care Unit. He was small for gestational age (SGA at the 5th percentile). Dysmorphic features were noted such as coarse facial traits, low implant of the ears, poor spontaneous motricity, hypertone of the lower limbs and coronal hypospadia.

During the first days of life, cerebral ultrasound and brain MRI confirmed partial agenesia of the corpus callosum and thickening of the lower portion of the quadrigeminal lamina with stenosis of the Silvio aqueduct and slight dilatation of the supra-tentorial ventricular system (Figure 1 A). Abdomen ultrasound confirmed bilateral hydronephrosis. Heart ultrasound was normal.

Urgent genetical investigation was performed: karyotype resulted normal (46, XY), Array-CGH revealed a non-specific area of homozygosity in the 9q31.1-31.2 region. For further diagnosis, exome study (Trio-Whole-Exome-Sequencing) identified the c.1130G>A variant (p.Arg377His) in exon 9 of the SMARCB1 gene. The variant is pathognomonic for Coffin Siris Syndrome.

In the meantime, mechanical ventilation was continued. Two unsuccessful attempts of extubation were performed (at 3 and 12 days of life) because of the onset of inspiratory dyspnea, desaturation and hypercapnia.

He presented complete dysphagia and was fed enterally through a nasogastric tube and parenteral nutrition, initially through the umbilical venous catheter and then a central line.

Lung Computerized Tomography (CT) was performed at 48 days of life, which excluded airway abnormalities. At two months of life, fibroscopy was then performed, which identified arytenoid edema: after a 7-day course of steroids and a resolution of the edema at a further fibroscopy, endotracheal tube was removed and respiratory support with High Flow Nasal Cannulae (HFNC) was initiated. He maintained HFNC for four weeks with fair stability of clinical parameters, adequate gas exchanges and rare episodes of dyspnea resolved by postural variations. At 3 months of life a polysomnography was performed, which showed many episodes of mixed hypopneae that triggered bradycardia. Therefore, Continuous Positive Airway Pressure (CPAP) was started. At

70 days of life the patient required intubation because of progressive worsening of respiratory acidosis. A trachea-bronchoscopy was performed which confirmed a pressure dependent trachea-broncho-malacia. At 4 months of life, he underwent tracheostomy and was started on full-syncronized ventilation.

For bilateral hydronephrosis, at 15 days of life he was started on antibiotic prophylaxis. At subsequent renal ultrasound monitoring, pathological shape and size, poorly differentiated and thinned parenchyma of the right kidney was identified, due to the presence of voluminous cysts; the left kidney presented a non-homogeneous parenchyma and reduced medullary cortical differentiation (Figure 1 E, F). At five months of life kidney scintigraphy was performed which found an obstructive uropathy at the right kidney and a reduced function of the left kidney (almost 30%). No vesicoureteral reflux was identified. He suffered one urosepsis episode at two months of life with isolation of Proteus Mirabilis at urinocolture. At 6 months of life an episode of Acute Kidney Injury occurred during de-hydration. Currently there is no surgical indication, and the antibiotic prophylaxis was stopped.

For complete dysphagia, Percutaneous Endoscopic Gastrostomy (PEG) was performed at 5 months of life (Figure 1B).

Further malformative aspects are mild bilateral mixed hearing loss associated with dysfunction of the brainstem acoustic pathway, for which hearing aids will be placed; medium-severe mitral insufficiency was detected at 6 months of age and he was started on diuretic therapy (furosemide and captopril, which was administered for four weeks). During hospitalization he suffered many infectious events. Immunologic function was tested, which resulted normal.

Brain MRI was repeated at 2 and 5 months of life (Figure 1 C, D): an increase of supra-tentorial ventricles was identified with no need for surgery. At 8 months, he presented spastic tetra-paresis characterized by extremely poor spontaneous motricity, hypertone of the four limbs (upper limbs in flexion, lower limbs in extension) and hypotone of the troncus, as well as complete dysphagia.

During mechanical ventilation the patient was sedated with fentanyl, midazolam and morphine. With suspension of sedoanalgesia, he presented episodes of agitation and poor adaptation to the devices. Therapy with delorazepam was started.

After eight months of hospitalization in the Neonatal Intensive Care Unit, the patient was transferred to a pediatric hospice with the aim of subsequent domiciliation. Quality of life, prognosis and life expectancy were discussed with the patient's parents and his physicians and a decision to not resuscitate was taken.

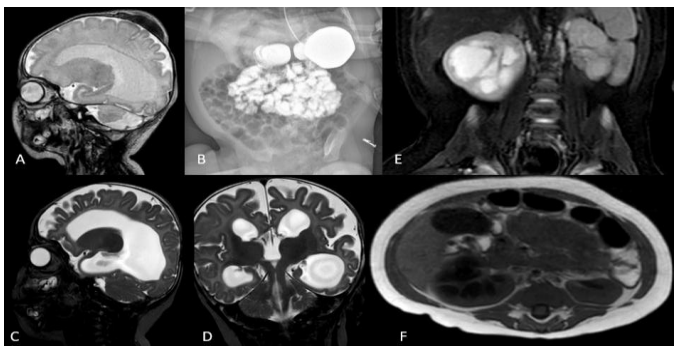

Figure 1: A: Brain MRI at 5 days of life. **B:** Placement of Percutaneous Endoscopic Gastrostomy. **C and D:** Brain MRI at 5 months of life. **E and F:** Abdomen MRI performed at 5 months of life

DISCUSSION

We report the case of a late preterm baby who was diagnosed with Coffin Siris Syndrome (CSS) at 2 months of age, due to a de novo mutation in SMARCB1. Mutations in SMARCB1 are responsible for 7-12% of all Coffin Siris Syndrome cases.[2,3,7] Mutations in SMARCB1 are associated with a more severe phenotype, growth impairment, more frequent kidney malformations, neurosensorial hypoacusia/deafness and a higher grade of development delay in comparison to other genotypes.[2,3,7] In comparison to previously described cases, our patient presents a very severe neurological impairment, severe kidney involvement and extreme airway malformation which required tracheostomy; this is the second case described in literature so far.[1]

In the case reported, in utero malformations, such as agenesia of corpus callosum and bilateral hydronephrosis, were identified at 27+6 weeks of gestation. Prenatal findings of Coffin Siris Syndrome are not frequent. Rarely, central nervous system or cardiac anomalies, intra-uterine growth restriction (IUGR), and microcephaly have been noted[2]. The most frequent in utero malformation reported is agenesia of corpus callosum[8-10]; it is due to midline glia aberrations due to an incomplete development of the brain midline.[11]

Since birth, one of the main key problems of this young patient has been airway management. He required mechanical ventilation since he was born, and when a pressure-dependent bronchomalacia was diagnosed, tracheostomy was performed. In literature, airway malformation such as tracheomalacia, laryngomalacia and difficult intubation have been described.[3,7,12] Only one case of tracheostomy has been reported.[1]

The patient presented since birth an abnormal neurological phenotype, such as poor spontaneous motricity and hypertone of the lower limbs. Brain ultrasound and MRI, performed within the first days of life, confirmed the agenesia of corpus callosum and a slight dilation of the lateral ventricles due to stenosis of the cerebral aqueduct. Such dilation progressively increased by the age of 5 months; neurosurgeons have chosen to date for "wait and see" approach. He has always presented a complete dysphagia.

Our patient has never suffered seizures; epilepsy is a frequent finding in patients affected by Coffin Siris Syndrome,[2] and an incidence as high as 80% has been reported in patients with SMARC1B mutations.[7] Mean age of seizure onset of three patients with SMARC1B mutation was 5.5 years in one study;[13] in such study the authors hypothesize that SMARCB1 is involved in dendrite growth, therefore its mutations might be responsible for the development of abnormal neuronal circuits, potential substrate for seizure development.

Delay in developmental milestones is always associated with CSS.[2] Sitting at 12 months of age, walking at 30 months of age and saying of first words at 24 months of age has been reported[2] SMARCB1 mutations are associated to severe intellectual disability. Our patient presented a severe developmental delay since the first days of life; at 7 months of life he presented severe delay in all milestones, with hypotonia of the truncus and hypertone of the four limbs. Prolonged hospitalization in an Intensive Care Unit, tracheostomy, and multiple infections probably worsened his neurological prognosis.

In 35% of patients (45% of SMARCB1 patients[7]) affected by CSS, renal and genitourinary malformations have been described, such as cryptorchidism, horseshoe kidney, hypospadias.[2] In our child, prenatal bilateral hydronephrosis was diagnosed, and confirmed by abdomen ultrasound after birth. Coronal hypospadias was

identified on the first day of life. A severe reduction in kidney function was diagnosed by kidney scintigraphy; the case was discussed with pediatric urologist, who gave no indication to perform surgery. He has already suffered one episode of Acute Kidney Injury.

During hospitalization, the patient has suffered many infections, such as urosepsis, gastroenteritis, and pneumonia. Immunological studies resulted normal. Such findings are reported in other cases of Coffin Siris Syndrome; no specific deficits have been identified.[1,2,7]

Finally, SMARCB1 germline and somatic mutations have been described in association with neoplasms, such as rhabdoid tumor predisposition syndrome[14] and schwannomatosis.[15]

CONCLUSIONS

Coffins Siris Syndrome is a rare neurological syndrome characterized by phenotypical heterogeneity, from mild cognitive impairment[16] to severe multi-organ compromise as in our patient.

A correct and early genetic diagnosis is essential to communicate to parents a realistic prognosis and to start an adequate therapeutic and comfort care.

Advances in the field of genetics allow us to identify pathologies that would otherwise be difficult to diagnose, especially those with extremely heterogeneous CSS presentation that most frequently manifests itself in a milder form.[17]

In addition to corroborating the diagnosis through genetic testing, the initial evaluation is also aimed at detecting comorbidities that might increase the level of disability and assessing the family environment and providing assistance for parents.

Management of CSS is aimed at fostering optimal intellectual development, avoiding complications, and detecting comorbidities. Multidisciplinary care is required, including physical and speech therapists, gastroenterologists, neurologists, cardiologists, nephrologists, pediatric physiatrist or orthopedist, ophthalmologist and audiology specialists.

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