

CASE REPORT

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Schaaf-Yang syndrome: A novel variant in *MAGEL2* gene in the first Brazilian preterm neonate

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ABSTRACT

Introduction: Schaaf-Yang syndrome is a rare genetic disorder first described in 2013. We aim to publish the first Brazilian case report of Schaaf-Yang syndrome as well as to describe the first variant p.Val701Glyfs*12 of a patient in a neonatal intensive care unit in a tertiary hospital in Belém, Brazil. **Case Report:** A preterm neonate patient 37-2/7 weeks, admitted to a tertiary private hospital in the North Region of Brazil, was promptly diagnosed with Schaaf-Yang syndrome and received the adequate clinical management. Clinical manifestations of the disease were associated to neonatal hypotonia, intellectual disability and developmental delay, hypogonadism, and hyperphagia. **Conclusion:** After evaluating potential and more commonly genetic diseases, a prompt and complete genetic assessment is helpful to establish a definite diagnosis of Schaaf-Yang syndrome and correlated diseases.

Keywords: Case report, Congenital, Genetic disease, In-born, Intensive care units, Neonatal, Newborn, Respiratory distress syndrome, Schaaf-Yang syndrome

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INTRODUCTION

First described by Schaaf et al. in 2013, Schaaf-Yang syndrome is an autosomal dominant pathology that manifests as a complex group of clinical symptoms and signs. These include intellectual disability and a wide spectrum of clinical and behavioral features, including low infant muscle tone, feeding incapacity, hyperphagia, followed by early overweight or obesity, hypogonadism, and short stature [1, 2]. This syndrome is usually life-limiting, frequently causing miscarriage with fetal akinesia and, for those who survive, it has been associated with moderate to high late disability [3]. Belated diagnosis in affected newborns is common, especially in undeveloped countries, where access to advanced genetic tools (whole-exome sequencing or single-gene Sanger sequencing) is limited. Furthermore, it is worth mentioning that this delay might be caused as Schaaf-Yang syndrome has similar characteristics to other genetic syndromes, such as Prader-Willi syndrome. Therefore, genetic testing stands as an important method to obtain an adequate differential diagnosis. We report a case of a 37-2/7 weeks preterm male patient with this rare syndrome.

CASE REPORT

A male preterm neonate weighting 2965 kg, measuring 50 cm, and with a head circumference of 35.5 cm was delivered by cesarean section at 37-2/7 weeks of gestation at the Hospital Maternidade Saúde da Criança (Child’s Health Maternity Hospital), Belém (Brazil) on November 13, 2019. Information regarding maternal prenatal care was unavailable. The Apgar scores were 4 and 7 at 1 and 5 minutes, respectively. Immediately after birth, the patient developed neonatal hypoxia, meconium aspiration syndrome, requiring life resuscitation at delivery wards and then admitted to the neonatal intensive care unit (NICU). The neonate had remarkable hypotonia, hyporeflexia, syndromic facies with micrognathism, single palmar crease, and short lower and upper limb(s).

The preterm neonate had non-consanguineous progenitors, without any noticeable genetic disorder(s). We promptly performed screening for inborn errors of metabolism, which was confirmed as negative, as well as a normal human karyotype (46, XY). In order to obtain a conclusive diagnosis of the patient’s condition and to offer the most appropriate clinical management, we performed whole-exome sequencing using Illumina technology (GRCh38 used as reference). The blood sample result after 24-days indicated the presence of the Schaaf-Yang syndrome, position chr15:23.645.643, variation C>CG, sequence p.Val701Glyfs*12 ENST00000650528 (Figure 1). The variant (p.Val701Glyfs*12) was confirmed by the Sanger method and was also identified in the neonate’s father.

The preterm neonate’s clinical features matched with those previously described in the literature, with a severe neonatal hypotonia, feeding issues, craniofacial

disproportion (Figure 2), dyspnea, caused by upper respiratory tract narrowing secondary to retrognathia, and glossoptosis. Other clinical features noted were: sustained tremor of lower limb, micrognathia with pits on the mental region, prominent genian area, smooth philtrum, lateral deviation of wrists, with single transverse palmar crease on the hands, rigid narrow thorax (Figure 3), and rhizomelic shortening of lower limbs (Figure 4). There were no severe body dysmorphic disorders (Figure 5).

Patient remained in NICU for three months and twenty-two days, with a multidisciplinary follow-up until hospital discharge. The patient was born hypotonic, with mild-to-moderate respiratory distress, and bradycardic, requiring intubation in the delivery room with positive pressure ventilation. Maternal progenitor had untreated leukorrhea history. The patient presented with mild jaundice, was kept on a zero diet and had overlapping cranial sutures. Transfontanellar ultrasound was normal. Due to a suspicion of early neonatal pneumonia, the patient started therapy with antibiotics and underwent several radiographs throughout the hospital stay to monitor the evolution of the patient’s clinical condition. He remained hypoactive and unresponsive to handling, requiring further karyotype assessment. After a week of hospitalization, he started to develop laryngeal stridor and a moderate-to-severe respiratory distress, which required an otorhinolaryngological evaluation. Because of bronchospasm, beta-2-adrenergic agonist and glucocorticoid were administered. A nasal endoscopy revealed glossoptosis.

In the second week of hospitalization, the patient presented worsening of respiratory distress and fever with progressive radiological worsening. Thus, we

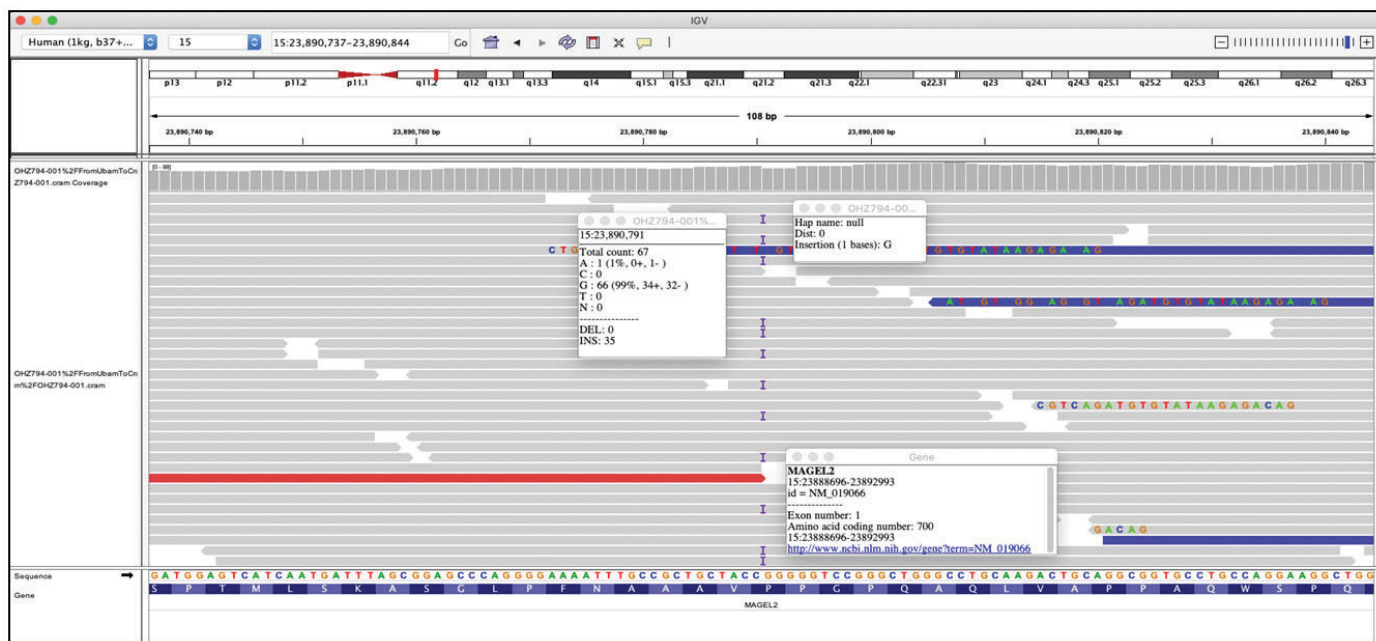


Figure 1: Integrative genomics viewer (IGV) visualization of variant *MAGEL2* in the whole-genome sequencing of the described patient.



Figure 2: Skull radiography showing a craniofacial disproportion.



Figure 3: Chest radiography showing a shortening of the chest and heterogeneous alveolar opacities in both lungs.

implemented the protocol of suspected sepsis, which required ventilatory support. During the night of the same day, he had cardiorespiratory arrest due to hypoxemia, which was reversed after a cycle of cardiopulmonary resuscitation and a single dose of adrenaline. He was then maintained on mechanical ventilation, antibiotic therapy, as well received beta-1 adrenergic and opioid analgesic. The medical team requested a red blood cell concentrate and central venous access with dissection of the right axillary vein.



Figure 4: Radiography of the pelvis showing bilateral femoral shortening.

In the third week, the evaluation of neuropaediatrics suggested suspicion of congenital arthrogyrosis or genetic/chromosomal syndrome; administration of anticonvulsant was recommended. The electroencephalogram showed no abnormalities. In addition, the ophthalmological evaluation was normal. In the evaluation of the geneticist physician, screening for metabolism errors was suggested. The karyotype was not yet available. At the evaluation of orthopedics with hip ultrasonography, the patient presented the type Ia hip in the Graf classification.

In the fourth week of hospitalization, a tracheostomy was needed due to the need for prolonged ventilation, along with a gastrostomy due to the need for enteral nutrition by tube. The patient had gastroesophageal reflux



Figure 5: Radiograph of the abdomen showing increased intestinal meteorism and distended ileal loops.

that improved due to gastrostomy. In the fifth week, we maintained O₂ support and macronebulization with beta-2 agonist and minimal enteral diet through the gastric tube. The patient had lesions with a hyperemic base with yellowish crusts on the dorsum and exulcerated lesions in the right inguinal and axillary region, suggesting impetiginized fungal infection. Therefore, we started a course of therapy with antibiotics, antifungals and began sepsis protocol once again.

In the sixth week, there was a reevaluation with a neuropediatrics, which suggested an investigation for hypotonic syndrome of neuromuscular origin; and anticonvulsant maintenance as a protective measure. Magnetic resonance imaging was normal, not excluding the hypothesis of central etiology. A hypothesis of congenital arthrogyriposis was ruled out. The patient improved his skin lesions. A skull radiograph showed craniofacial disproportion. An evaluation of home care was suggested. The patient remained under routine and symptomatic care. In the ninth week of hospitalization, there was a reassessment of medical genetic specialists. The karyotype showed 46, XY; and the profile for metabolic diseases was negative. The electroencephalogram remained normal, as well as the neuroimaging. For the diagnostic definition of the monogenic condition, it was suggested to perform a complete exome sequencing exam.

In the 14th week of hospitalization, the central venous access was removed. The result of the DNA test showed Schaaf-Yang syndrome. The patient remained in hospital for another three weeks with additional diagnoses of

glossoptosis, narrowing of the airways, late neonatal infection, and inhaled corticosteroids in late pneumonia. In the 16th week, while the patient waited to be taken to home care and underwent training to leave ventilatory support, he developed central cyanosis and seizure with tonic-clonic movements of limbs and tongue tremors. Ventilation was maintained through the tracheostomy and the gastric tube was closed.

In the last week of hospitalization, the patient ended the antibiotic therapy, trained for home care. He remained on macronebulization and on a gastric tube diet through gastrostomy. He was discharged with a body mass of 5155 g, length of 52 cm, and head circumference of 40 cm. He evolved well and without complications after discharge. Two months after discharge, he had an episode of pneumonia, requiring hospitalization in the intensive care unit (ICU) for five days, being discharged and as June 8, 2020 the patient has been progressing adequately. During the hospital discharge, the parents were advised of the continuous need for medical consultations and the importance of a multiprofessional healthcare team.

DISCUSSION

Schaaf-Yang syndrome is a very rare neurological genetic disease, with a worldwide prevalence of less than 1/1,000,000 [4]. It is usually life-limiting and incurable, requiring life-long specialist management. It is commonly first seen in neonatal patients, with less than 160 cases reported worldwide. As children grow, late manifestations are noticed and a more complicated stage of the disease is established, unless prior diagnosis is achieved with adequate delivery of treatment is offered. This is the first case of Schaaf-Yang syndrome reported in Brazil. The ongoing political and economic crisis makes access for appropriate diagnostic resources and adequate medical intervention challenging. However, despite inherent difficulties, the medical team involved in this case made the diagnosis as early as possible (in approximately 100 days). Furthermore, this is the first case described in the literature with the variant p.Val701Glyfs*12 (c.2099_2100insC or c.2099dupC).

Early diagnosis of Schaaf-Yang syndrome is fundamentally dependent on genome sequencing. Nevertheless, a comprehensive physical and clinical examination is the primary assessment that physicians can perform in suspected cases. It is necessary to differentiate neonates affected by Schaaf-Yang syndrome, Prader-Willi syndrome, Chitayat-Hall syndrome, and Freeman-Sheldon syndrome [5]. The differential diagnosis of Schaaf-Yang syndrome is difficult to make due to strikingly similar clinical manifestations in the aforementioned diseases, such as major neonatal hypotonia, breathing and feeding difficulties, intellectual deficit and developmental delay, behavioral changes

and hypogonadism, recognizable contracture, small mouth, and narrow eyelid fissures [5–8]. However, in Schaaf-Yang syndrome cases, there are thought to be a higher frequency of contractures, especially of the interphalangeal joints, more severe autistic spectrum disorder, developmental delay, and more severe intellectual deficit [2, 5–8]. It seems that in Schaaf-Yang syndrome, patients have worse hypotonia, which can be associated with the emergence of feeding difficulties and decreased gastric motility, motor delays, respiratory disorders, and skeletal abnormalities [2]. Additionally, compared to Prader-Willi syndrome, it is thought that there is a lower frequency of hyperphagia and subsequent obesity [5, 9]. Only 22% of patients with Schaaf-Yang syndrome develop excessive weight gain, and in 25% hyperphagia is observed [9]. Studies suggest that joint contractures may be the most pathognomonic finding of Schaaf-Yang syndrome, which would help in the clinical differentiation from Prader-Willi syndrome [3, 8]. As far as severity is concerned, a more serious condition may be related to a c.1996delC mutation [9].

The *MAGEL2* is heterozygous and the allele inherited from the mother does not express and encode any abnormal protein. Therefore, maternal inheritance does not generate phenotypes, making it clinically irrelevant. On the other hand, the paternally inherited allele is expressed, therefore it is functional. Mutations in this locus, regardless of its nature, will lead to potentially pathogenic phenotypic changes [10]. It was established that our patient expressed the paternal copy of *MAGEL2*. Given our patient's clinical features, the most commonly described syndromic characteristics were also reported. For instance, the neonate was born with severe hypoxia, meconial aspiration syndrome, bradycardia, and hypotonia. In addition, the patient needed, even in the delivery room, ventilatory support with orotracheal intubation and mechanical ventilation, and required food support with an orogastric tube. Previous cohorts have reported that 58% of patients with Schaaf-Yang syndrome needed intubation, 55% mechanical ventilation, and 18% require tracheostomy [11]. In addition, 93.75% of these patients needed some type of nutritional support and 97% of the patients had feeding difficulties, 75% of whom required a nasogastric tube, and 53% a gastrostomy tube.

CONCLUSION

In conclusion, we present a novel *MAGEL2* variant (p.Val701Glyfs*12) in a neonatal patient with typical clinical presentations of Schaaf-Yang syndrome. This syndrome has a wide number of phenotypes contributing to difficulties in differential diagnosis. Our understanding of the plethora of way the disease can manifest is progressively improving, however, requires future investigation.

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Author Contributions

Guilherme Augusto Lira Ribeiro de Andrade – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Thaís Barros de Oliveira Silva – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Anna Boath – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Katiane da Costa Cunha – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Aurimery Gomes Chermont – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.

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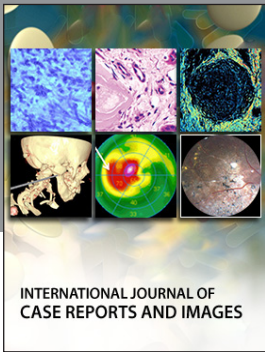
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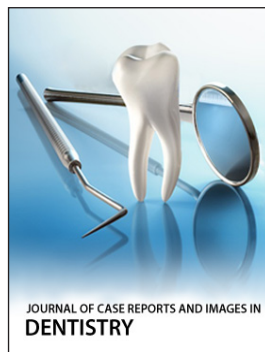
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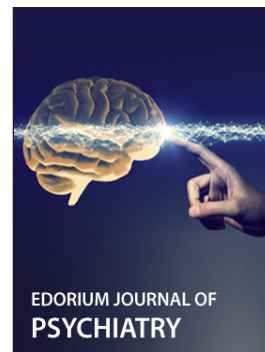
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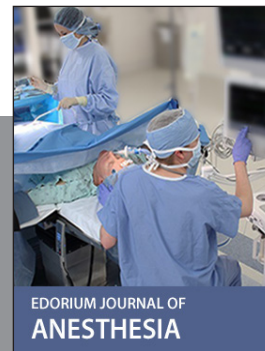
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