Anatomical variations linked to Primrose Syndrome: case report

Variações anatómicas ligadas à Síndrome de Prímula: relato de caso

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ABSTRACT
Primrose syndrome, also called Primrose Syndrome, is a unique autosomal dominant condition caused by heterozygous variants of the type missense in the ZBTB20 gene that lead to a rare genetic disorder. Its main features include an intellectual disability, typical facial properties, abnormalities of the callous body, and autistic features. Other frequent clinical associations include sensorineural hearing loss, hypotonia, macrocephaly, behavioral and dyslexic problems, and glucose metabolism disorders with insulin-resistant diabetes, and loss of distal muscle mass occurring in adulthood. The disorder is caused by functional dysregulation of ZBTB20, a transitional repressor that controls energy metabolism and development alums. We report the case of a man diagnosed with Primrose syndrome, emphasizing its main characteristics and anatomical variations. He is a 30-year-old Brazilian who has a phenotype similar to cases of Primrose syndrome, however, with additional characteristics of ectopic calcifications and progressive muscular and skeletal abnormalities. The work was approved by the Research Ethics Committee under the number 4.911.653.

Keywords: Primrose Syndrome, ZBTB20, ectopic calcification, intellectual disability, anatomical variation.

RESUMO
A síndrome de Primrose, também chamada Síndrome de Primrose, é uma condição autossómica dominante única causada por variantes heterozigóticas do tipo missense no gene ZBTB20 que conduzem a uma doença genética rara. As suas principais características incluem uma incapacidade intelectual, propriedades faciais típicas, anormalidades do corpo caloso e características autistas. Outras associações clínicas frequentes incluem perda auditiva neurossensorial, hipotonia, macrocefalia, problemas comportamentais e disléxicos, e perturbações do metabolismo da glicose com diabetes resistente à insulina, e perda de massa muscular distal que ocorre na idade adulta. A

perturbação é causada pela desregulação funcional do ZBTB20, um repressor de transição que controla o metabolismo energético e os alcances de desenvolvimento. Relatamos o caso de um homem diagnosticado com Síndrome de Prímula, enfatizando as suas principais características e variações anatómicas. É um brasileiro de 30 anos de idade que tem um fenótipo semelhante aos casos de síndrome de Prímula, contudo, com características adicionais de calcificações ectópicas e anomalias musculares e esqueléticas progressivas. O trabalho foi aprovado pelo Comité de Ética em Investigação sob o número 4.911.653.

Palavras-chave: Síndrome de Prímula, ZBTB20, calcificação ectópica, incapacidade intelectual, variação anatómica.

1 INTRODUCTION

Primrose Syndrome (PRIMS) is a very rare autosomal dominant disorder in the ZBTB20 gene, first described by physician David Primrose in 1982. In 2014, the pathogenic heterozygous variants in ZBTB20 demonstrated to cause Primrose Syndrome (Cordeddu et al., 2014). ZBTB20, located in the 3q13.31 chromosomal position, is responsible for encoding a zinc finger protein that has five C2H2 domains (ZNFI-ZNFV) and a BtB N-terminal domain (Broad Complex, Tramtrack, Bric a brac). This protein plays an essential role as a transcriptional repressor that interacts with genomic DNA through its ZnF domains and is also implicated in the regulation of glucose metabolism, immune responses, fetal liver development, somatic growth, postnatal growth and neurogenesis regulation (Sutherland et al, 2009; Xie et al, 2010; Zhang et al, 2012).

This syndrome has a variable phenotype characterized by hypotonia, cognitive delays, excessive postnatal growth, in addition to a characteristic facial appearance, with deep eyes, narrow and often lower-sloping palpebral fissures, ptosis, depressed nasal bridge, and macrocephaly with or without tall stature. Other reported clinical features include loss of distal muscle mass, calcified tweezers, hearing loss, cataract, hypothyroidism, and sparse hair of the body and face (DSR e Dias, 2022; YC e Prieto, 2022). Calcified external ears are also frequently present (Carvalho and Speck-Martins, 2011; Casertano et al., 2017; Cordeddu et al., 2014; Mattioli et al., 2016). To date, there are 23 individuals with molecularly confirmed PRIMS in the literature (Alby et al, 2018; Casertano et al, 2017; Cleaver et al, 2019; Cordeddu et al, 2014; Grímsdóttir et al, 2018; Hersh et al, 2015; Mattioli et al, 2016; Stellacci et al, 2018). The aim of this article was to describe the presence of Primrose syndrome and morphofunctional changes caused by this syndrome in a diagnosed individual.

The individual described is a 30-year-old Brazilian male with facial features typical of the syndrome such as: mandibular protusion, deep eyes, down-tilted palpebral fissures, wide, calcified ear pavilions, and wide forehead. However, in addition to the classical characteristics of the syndrome already described in the literature, it presents other specific characteristics, including persistence of *cavum septum pellucidum* and *cavum vergae*, arteriovenous malformation in the left auricular pavilion, progressive *genu valgum*, deficit in the function of the median nerve (brachial plexus), cranial deepening at the level of the lambdoide suture, imitation communication and gestures with family members and reflex syncope. This individual reinforces the singular phenotype of this rare disorder, which is the second reported case of Primrose Syndrome in Brazil.

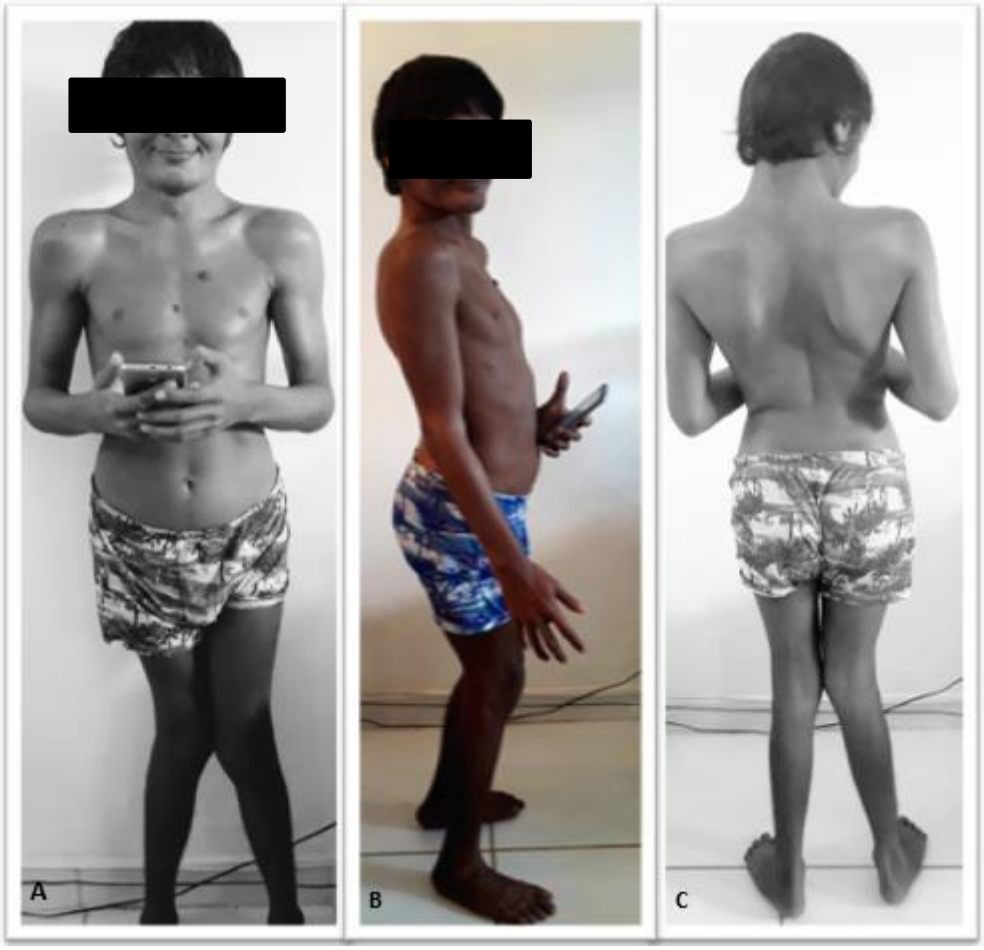
2 CASE REPORT

The individual (F. A. N.) is a 30-year-old man born by cesarean section after a pregnancy without complications and/or complications during or after his birth. It is the fourth of five children (with siblings without other congenital syndromes or pathologies) of father and mother who were 41 and 39 years old, respectively, at the time of their birth. His birth weight was 3.2 kg and the length was 48 cm. At 6 months he was able to sit without assistance and at 18 months strabismus was observed. At 1 year, he weighed 10kg and 81 cm in length; at 6 years he weighed 19 kg and averaged 100 cm. Cognitive and developmental delays and progressive hearing loss were diagnosed throughout childhood, and hearing loss was treated with the use of in-ear hearing aids from 7 to 19 years, a period in which progressive auricular calcification began to be observed.

His family reported a series of fainting during the first childhood, especially when exposed to stress and fainting was accompanied by hyperventilation and cyosis, followed by loss of consciousness. These episodes completely disappeared after childhood, even without specific treatments, however, he suffers from reflex syncope (fainting at the age of life).

At the age of 18, the family members noticed loss of distal muscle mass in the knees, shoulders, proximal and distal phalanges of the hands and feet, which progressively worsened over time, causing difficulty in locomotion. His skeletal abnormalities were diagnosed as lumbar hyperlordosis and genu valgum,initiating physical therapy treatmentthat lasted for 5 years, until, at age 21, his mother reported aggressive behavior. The individual was diagnosed with autistic spectrum, and initiated a risperidone-based treatment that persists to date.

Figure 2 - Body images revealing the standing posture of individuals with Primrose syndrome. It is possible to observe and highlight the shoulders inclined forward (A). In B, contracture is observed in knee flexion and excavated chest (*Pectus Excavatum*) which may be a factor for inclined shoulders. It can also be highlighted in C the large and well evident scapulars besides scoliosis and light lordosis.

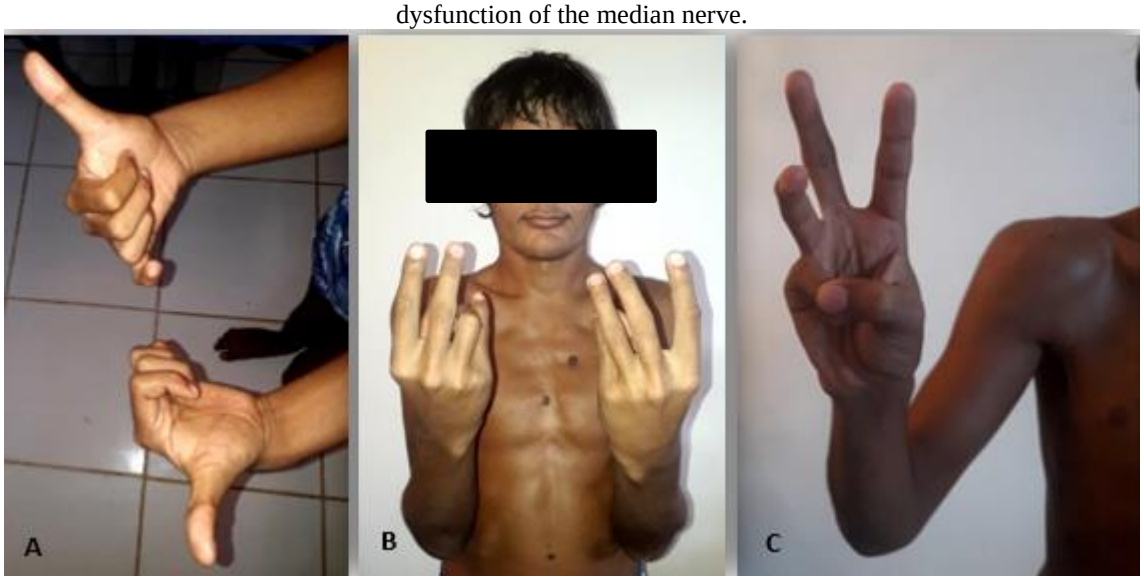


At the age of 29, her initially moderate hearing loss progressed to a severe condition, with calcification of her external ears. He was later diagnosed with an arteriovenous malformation in the left auricular pavilion due to calcification, with severe venous and arterial bleeding with risk of imminent death in case of arterial rupture.

Currently, the individual weighs 59 kg, with 163 cm in length and head circumference of 56 cm, presenting anatomical features of Primrose Syndrome, which are brachycephaly, wide forehead, wide and calcified ear pavilions, ptosis, deep eyes, prominent palatine torus, hearing loss, delay in intellectual development and sparse hair throughout the body. In addition, the individual presents unique characteristics such as cranial deepening at the level of the lambdóide suture, delay in the development of male sexual characters, mutism and development of communication by imitation and gestures with family members. It was observed a difficulty to completely open the hands, and to

flex some specific fingers for the performance of common gestures, indicating a possible damage to the median nerve of the brachial plexus or inrrigerations of the metatarso-phalangeal and interphalangeal joints.

Figure 3 - Images of upper limbs in individuals with Primrose syndrome. These images highlight the patient's difficulty in performing some signals with his hand (example: symbolizing number three and rocker sign). In A, there was a certain difficulty in keeping the first and fifth fingers extended and the other fingers flexed simultaneously. In images B and C, when performing finger flex to represent number 3, weobserved thenon-complete extension of the fourth finger (ring). It may infer possible injury or dysfunction of the median nerve.



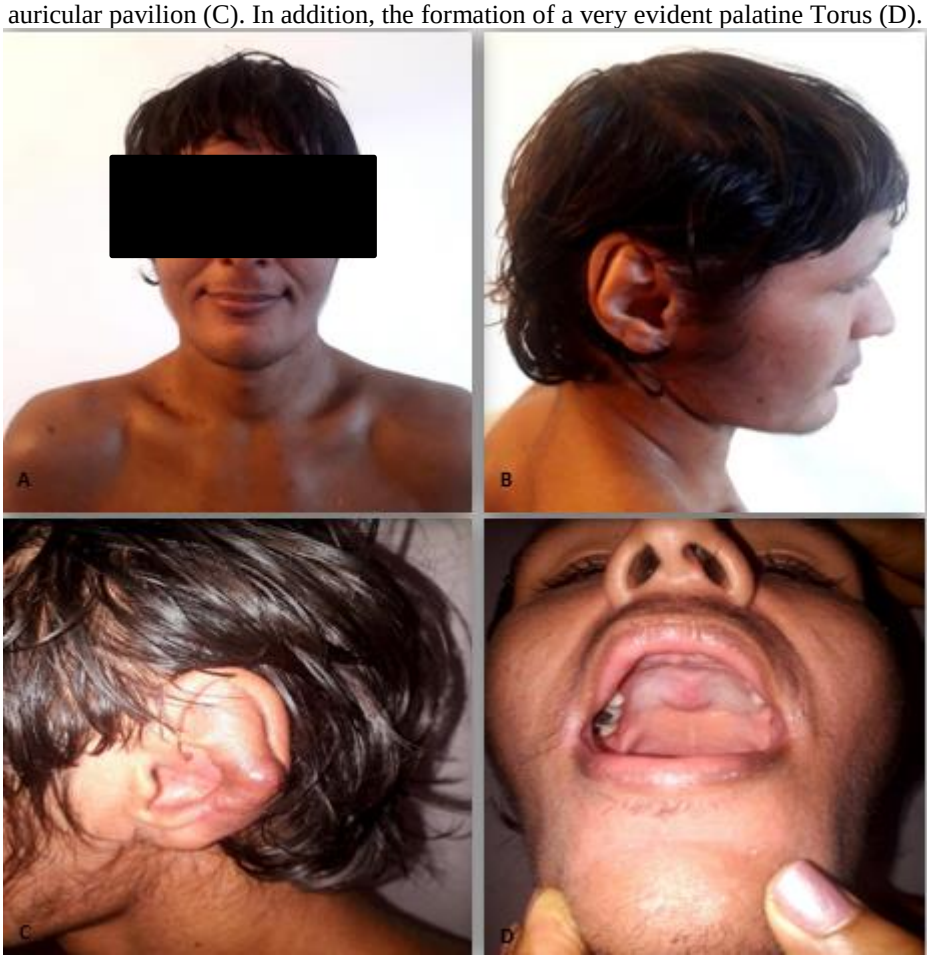
3 DISCUSSION

Recognized as a nosological entity for the first time for more than 35 years (Primrose, 1982), Primrose Syndrome is a rare genetic condition characterized by cognitive deficits often associated with autism spectrum disorders and specific facial features.

The characteristics most attributed to the syndrome include: large and calcified external ears, calcified tweezers, cerebral calcification (Alby et al, 2018; Carvalho and Speck-Martins, 2011; Casertano et al, 2017; Cordeddu et al, 2014; Mattioli et al, 2016), small mouth, deep eyes, large forehead, macrocephaly, ptosis, depressed nasal bridge, sparse hair on body and face, and jaw decay (Battisti et al, 2002; Collacott et al, 2008; Lindor et al, 1996; Mathijssen et al, 2006; Primrose, 2008 Dallal and Espay, 2010; Primrose, 1996, Hennekam, 2006; Stellacci et al, 2018). Of these characteristics described, the individual F. A. N., 30 years old, presented most of them, corroborating the findings in the current literature.

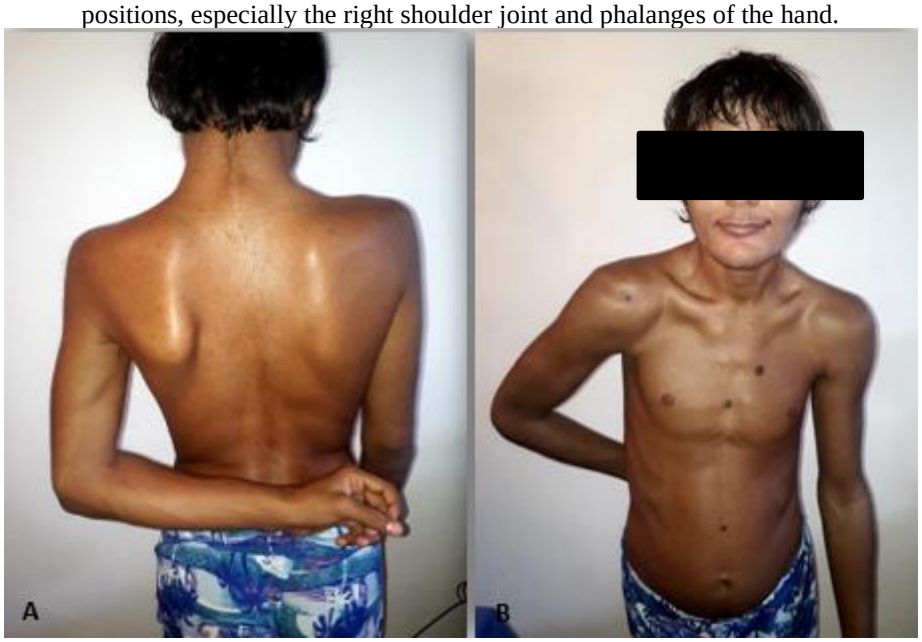
In the studied individual, we highlight some progressive signs and symptoms of Primrose Syndrome, such as hearing loss, genu valgum, muscular atrophy in the main joints of the limbs (elbow, ankle, knee and phalanges), cataracts, hypothyroidism, glucose metabolism disorder and the onset of diabetes, these findings are corroborated by several studies published in the literature (Battisti et al., 2002 ; Dallal, Leslie, Gilbert 2010; Lindor, Hoffman and Primrose, 1996; Posmyk et al., 2011; Oak & Speck-Martins, 2011). A cystic bone lesion was observed in four patients reported [Primrose, 1982; Mathijssen et al, 2006; Dallal et al, 2010], in addition to the development of *torus palatinus* (Collacott et al, 2008; Dallal et al, 2010; Mathijssen et al, 2006; Primrose, 2008) ectopic, brain and auricular calcifications. In the individual of the study in question, this calcification gave rise to an arteriovenous malformation in the left auricular pavilion.

Figure 1 - Facial features in an individual with Primrose Syndrome. Image A of the patient in the anterior view evidencing characteristic facial features such as macrocephaly, ptosis and deep eyes. It is also observed the wide and calcified right ear pavilion (B) and an arteriovenous malformation in the left auricular pavilion (C). In addition, the formation of a very evident palatine Torus (D).



The clinical case reported presented additional characteristics of Primrose Syndrome, which have not yet been reported in the literature as skeletal and muscular abnormalities, such as: stiffness of the shoulder and elbow joints revealing a poor posture when performing simple movements, besides presenting difficulty in moving some fingers of the hand (indicator, middle and ring), due to a possible damage or malformation of the median nerve of the brachial plexus, progression of *Genu valgum*, alacrimia, appearance of arteriovenous malformation in the left auricle pavilion with disruption of the left auricular artery and left auricular vein. Emphasizing that these described anatomical and physiological changes are progressive throughout the individual's life. However, the reported syndrome carrier did not develop any of the typical features of Primrose syndrome, such as alteration in glucose metabolism and the onset of diabetes during adulthood.

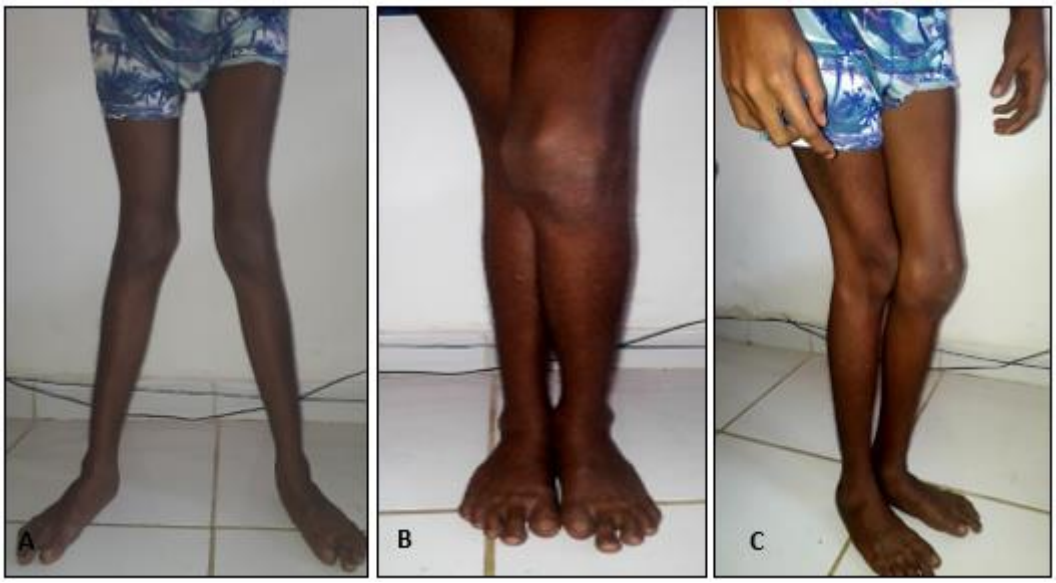
Figure 4- Trunk images in an individual with Primrose syndrome. On the other hand, the images of trunk A B show a joint stiffness of the shoulder and elbow, which hinders certain movements and common positions, especially the right shoulder joint and phalanges of the hand.



The cranial sinking at the level of the lambdóide suture follows the entire course of it, so it is not yet known for sure its true cause, however, it may be associated with poor closure of this suture (craniosytosis). In addition, the first short metatarsis and alacrima have not been previously described in cases of PRIMS, although these findings may be coincident (Decherchi, 2005; Hersh et al, 2015). The *genu valgum* is also progressive, along with the loss of muscle mass, causing pain and difficulty in locomotion increasingly evident, and may lead to the use of wheelchairs permanently. Another very

evident feature refers to its delay in physical development and aging. Yes, even though he is 30 years old, he still has physical traits of an 18-year-old man and psychological of a 3-year-old boy.

Figure 5- Images of lower limbs in individuals with Primrose syndrome. Front and profile images that highlight the patient's posture due to the axis deviation caused by Genu valgum. From the front with the legs open (a) it is easy to observe a curvature to the lateral of these limbs, with bony protrusion present in the medial part of the knee, forming between the thigh and the leg an open angle with projection of the foot out (*Genu valgum*). In addition, in order for the patient to be able to join the feet next to each other, the left knee is always in front of the right (B C).



The small number of cases described in the literature may raise questions about the real definition and concept of this syndrome, however, all reported patients have an extremely similar pattern of facial features. Demonstrating that all patients have a singular phenotype, characteristic of the syndrome, in addition to recurrent clinical abnormalities in all cases. The potential cause of PRIMS may be related to one of several mechanisms that control cartilage matrix calculation. A disorder in calcium metabolism may be an important factor in explaining ear calcification and has been suggested as a possible cause of Primrose syndrome (Mathijssen et al., 2006).

4 CONCLUSION

Primrose Syndrome is a rare genetic disorder, little known in the medical literature, related to an autosomal dominant mutation syndrome and therefore the cause of it is not known. We describe and illustrate the general and specific anatomical characteristics in one of the older individuals with the Syndrome today, associating with several important clinical correlations never described in the literature such as

craniosynostosis, mutism, arteriovenous malformation, reflex syncope, possible median nerve dysfunction, alacrima, etc. The few published cases only reinforce the lack of studies describing the anatomical and physiological characteristics of the syndrome, being necessary to help determine its early diagnosis, incidence and treatment, helping families and professionals who do not have knowledge about its anatomical characteristics and extreme behaviors associated with the syndrome, thus providing a better definition and understanding of this condition and enabling a better treatment for the individuals who fit the characteristics of the family. A great advance in this theme can come from a standardization of the main characteristics and clinical manifestations proven and associated with this syndrome in order to facilitate the diagnosis and treatment of the same, besides adding more knowledge to the medical literature and scientific community, facilitating the search and understanding for researchers and family members.

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