





Terminal deletion of the short arm of chromosome 6 (6P25.3P24.3): a literature review and case report of a Brazilian child

Deleção terminal do braço curto do cromossomo 6 (6p25.3p24.3): uma revisão de literatura e relato de caso de uma criança brasileira

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ABSTRACT:

Introduction: Deletion syndromes are rare events in clinical practice. A chromosomal deletion occurs when segments of genetic information are missing on a particular chromosome or more. The absence of some genes implies varied phenotypes, which detailed explanation is not fully elucidated yet. **Objective:** Report the case of a child with a terminal segment deletion of 8,9 Mb on the short arm of chromosome 6 (in 6p25.3p24.3) **Methods:** This case report was approved by the Ethics and Research Committee of the institution. For its preparation, the exam data provided by the patient's family were added from prenatal to early childhood and the discussion with professionals related to the case. **Results:** B.A.G., a two-year-old female child, the only daughter of non-consanguineous parents, no family history of similar diseases. She was born by premature cesarean section (GA: 35 weeks), presenting Dandy-Walker malformation, Fallot tetralogy, head circumference in the 97th percentile, and syndromic facies, with hypertelorism, low implantation of the ears, and opacity of both lenses. **Conclusion:** Deletions on chromosome 6 are a very rare genetic alteration. Until 2004, there were only 43 cases in the medical literature, excluding ring chromosome 6 anomalies³¹. Regarding the terminal deletions of the short arm, this case specifically - 6p24pter - was associated with developmental delay, brain malformations, abnormalities in the anterior chamber of the eye, hearing loss, and abnormalities in the ear, micrognathia, and heart diseases²⁵.

Keywords: Rare diseases, Congenital abnormalities, Chromosome deletion, Neonatal prematurity, Tetralogy of Fallot.

RESUMO

Introdução: As síndromes de deleção são eventos raros na prática clínica. A deleção cromossômica ocorre quando segmentos de informação genética são perdidos em um ou mais cromossomos. A ausência de alguns genes implica em fenótipos variados, cuja explicação detalhada ainda não está totalmente elucidada. **Objetivo:** Relatar o caso de uma criança com deleção de segmento terminal de 8,9 Mb do braço curto do cromossomo 6 (em 6p25.3p24.3) **Métodos:** Esse relato de caso foi aprovado pelo Comitê de Ética e Pesquisa da Instituição. Para sua elaboração, foram adicionados os dados de exames fornecidos pela família do paciente desde o pré-natal até a primeira infância e a discussão com profissionais relacionados ao caso. **Descrição do Caso:** B.A.G., criança de dois anos, sexo feminino, filha única de pais não consanguíneos, sem antecedentes na família de doenças similares. Nasceu por cesárea prematura (IG 35 semanas), apresentando Síndrome de Dandy-Walker, tetralogia de Fallot, perímetro cefálico no percentil 97 e fácies síndrômica, com hipertelorismo, baixa implantação das orelhas e opacidades do cristalino bilateralmente. **Conclusão:** As deleções no cromossomo 6 são alterações genéticas de grande raridade. Até 2004, existiam apenas 43 casos na literatura médica, excluindo a anomalia do cromossomo 6 em anel³¹. No que se refere às deleções terminais do braço curto, a do caso em questão - 6p24-pter - foram associadas o atraso no desenvolvimento, malformações cerebrais, anormalidades na câmara anterior do olho, perda auditiva, anormalidades no ouvido, micrognatia e cardiopatias²⁵.

Palavras-chaves: Doenças raras, Anormalidades congênicas, Deleção cromossômica, Prematuridade; Tetralogia de Fallo.

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INTRODUCTION

Deletion syndromes result from the loss of parts of the chromosome, which causes a chromosomal imbalance that can be partial or total, affecting more than one gene. These can be originated from the loss of genetic material during the formation of a ring chromosome, which is named like this because they have a circular shape as a result of breaks in their short and long arms and subsequent bond of the fractured extremities⁽¹⁾. This is because the alteration is the result of the breakdown of telomeres (structures that have genes located at the end of each chromosome) of the short and long arms of a filament chromosome.

Thus, a mutation can affect both autosomal and sexual chromosomes² and, depending on the number of deleted genes, there are different phenotypic manifestations, and interestingly, it is also found in humans with a normal phenotype. The larger the size of the basic chromosome in the formation of the ring, the greater the instability of the ring and the growth retardation in the affected person³. Therefore, cytogenetically specific autosomal deletions can cause severe congenital anomalies and/or physical and intellectual disabilities, implanting an incidence of about 1:7,000 born⁴. The severity of the syndrome will depend on the degree of involvement of the chromosomal deletion.

The history of deletion Syndrome on chromosome 6 demonstrates that these are rare events in the population⁵⁻¹². Until 2004, there were only 43 cases in the medical literature, excluding anomalies of ring chromosome 6. Of these, only ten cases described interstitial exclusions with the entire segment 6p22, 6p22.2 - p25.2 or 6p24 - p25¹³⁻²³.

In addition to being rarely reported events, partial deletions of chromosome 6 constitute a varied clinical phenotype. The clinical phenotype described in general for the syndrome presents mental retardation, microcephaly, abnormal sutures, wide nasal bridge, several anomalies of eyes and ears, short neck with excessive skin folds, and normal weight and length at birth^{5,24}. The clinical changes most related to the 6p24-pter deletion were associated with developmental delay, brain malformations, abnormalities in the anterior chamber of the eye, hearing loss, abnormalities in the ear, micrognathia, and heart disease^{5,25}. Patients with

greater and minor deletions that overlap this region are described in the Database of Genomic Variation and Phenotype in Humans using Ensembl Resources (DECIPHER), an interactive web-based database that incorporates a set of tools designed to assist in the interpretation of genomic variants. It contains information on the genomic variations of DNA samples from more than 35,000 patients, allowing comparisons and analyses of these data, presenting variable clinical pictures including, among others, cardiac malformations and glaucoma. Similar deletions have not been documented in the general population²⁶.

In view of the rarity of the genetic deletion syndrome on chromosome 6 and the relevance of its description to collaborate with future diagnoses or differential diagnoses, the objective of this study is to describe a clinical case, very rare and difficult to diagnose, in the case of a chromosomal alteration in a child with a deletion of the terminal segment of 8.9 Mb (Megabases) of the short arm of chromosome 6 (in 6p25.3p24.3).

METHODOLOGY

The present study was developed in 2019 at Universidade Federal do Pampa (UNIPAMPA), Uruguiana/Rio Grande do Sul campus, by medical students, under the guidance of university professors, including a physiotherapist and a pediatrician.

The accomplishment of this work started with the submission of the project at the Plataforma Brasil. With the acceptance of the ethics committee, the patient's mother was invited to participate in this case report, allowing her complete independence to deliberate on ways she would feel more comfortable conducting and assisting the study. With a positive response, we scheduled a group meeting to collect the patient's history and clinical examinations (B.A.G.) throughout her treatment.

Hereafter, we started extensive research on some case reports related to the chromosomal deletion that our patient presents, filtering information and gathering together in a discussion in this work. The primary purpose was to share a genetic case of an extreme rarity with the scientific community, aiming to clarify the syndrome of

terminal segment deletion of 8.9 Mb on the short arm of chromosome 6 (in 6p25.3p24.3) and discuss better procedures to manage the case.

Description of the case

Two-year-old female child, only daughter of non-consanguineous parents, with no family history of similar diseases. She was born by cesarean section due to obstetric indication, premature with 35 weeks, birth weight 2.444g, Apgar 5/9, assisted by a neonatologist. She had syndromic facies at birth, with hypertelorism, low implantation of the ears, macrocephaly, and opacities of the lens bilaterally. Neonatal screening tests did not show any abnormalities.

The syndrome was investigated by molecular analysis, with DNA extraction from the patient's peripheral blood sample when she was one mon-

th old, and her diagnosis was made at two months old. The exam for it was the SNP-array, which allows the investigation of DNA sequences to detect duplications and deletions of genomic segments. The exam identified a chromosomal alteration: the terminal deletion of the 8.9 Mb segment of the short arm of chromosome 6 (in 6p25.3p24.3), which can be seen below (Figure 1). The deleted segments overlap with the 6p microdeletion syndrome region (OMIM #612582; chromosome 6pter-p24 deletion syndrome), a contiguous deletion syndrome that presents a variable clinical, but may have recognizable phenotypes, once they follow patterns of malformation, such as hypertelorism, descending palpebral fissure, flattened nasal bridge, and Dandy-Walker syndrome²⁷. Therefore, the 6pter-p24 deletion detected on the test explains the occurrence of the patient's clinical condition reported here in this study.

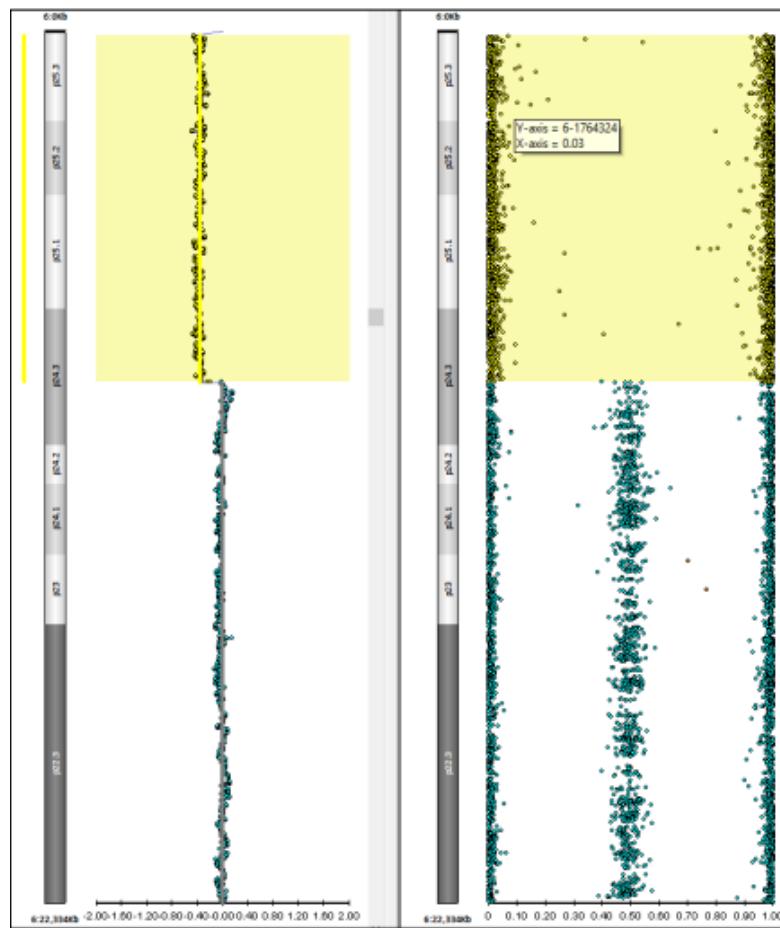


Figure 1: Profile of the Copy number (left) and SNP genotyping (right) of the short arm of chromosome 6, showing the terminal deletion in 6pter-p24.3

The diagnosis of hydrocephalus and Dandy-Walker malformation occurred during the intrauterine period and was immediately confirmed after her birth, presenting head circumference at the 97th percentile. In the first postnatal month, fenestration of the intrathecal cyst was performed, with emptying of hypertensive hydrocephalus, by microsurgery for intracranial tumors. After one month, a surgery was made to perform the ventriculoperitoneal shunt, which characterizes the reduction of extra-axial collections of the anterior fossa. Due to hydrocephalus, the patient presents generalized hypotonia and motor repertoire with little movement variability. She was referred to physiotherapy, where a motor evaluation was performed using the Alberta scale (AIMS), concluding a significant delay in motor development. From then on, the child was accompanied by physical therapists weekly.

Congenital glaucoma was diagnosed after the patient's birth. A bilateral trabeculotomy for decompression was performed in the first postnatal month. Close to one year of age, the patient was submitted to a fistulizing antiglaucoma surgery.

In the third trimester of life, the patient was hospitalized for epilepsy refractory to management with several anticonvulsants, such as oxcarbazepine and levetiracetam. The control of the crisis was only achieved with the use of phenobarbital and valproate

After seizure control, she underwent gastrostomy with fundoplication. Today, at the age of 2, she remains with gastrostomy.

About the tetralogy of Fallot presented by the patient, a ventriculoseptoplasty and enlargement

of the right ventricular outflow tract with preservation of the pulmonary valve was performed approximately two years postnatally.

The orthopedic follow-up was initiated in the second postnatal trimester of the patient by anteroposterior and lateral radiography of the spine. The findings revealed dorsal scoliosis of the right convexity, with rotation of the vertebral bodies from T7 to T11 to the right, dorsal vertebral bodies in the center of the scoliotic curvature, and dorsal kyphosis. Close to 2 years of age, the patient was admitted for a plaster cast based on the Mehta angle calculation. Today the patient is still using the instrument after adjustments and being accompanied by physiotherapists.

DISCUSSION

This study aimed to report the case of a child with a deletion of the 8.9 Mb on the terminal segment of the short arm of chromosome 6 (in 6p25.3p24.3). It is a rare pathology and, therefore, difficult to diagnose. The children affected by this syndrome often show severe psychomotor delay, congenital heart diseases, hypertelorism, and defects in the structure of the eyes. A comparison study was made by Mirza et al., 2004 to demonstrate similarities and differences between six children affected by genetic deletions at the same chromosome but in different locus.

The specific anomalies of the reported cases on Mirza et al., 2004, and our case (B.A.G) are summarized in **Table 1**.

Table 1

COMPARISON OF GENOTYPE AND PHENOTYPE BETWEEN THE CASE REPORTED HERE (B.A.G) AND CASES PREVIOUSLY DESCRIBED IN THE LITERATURE:

	B.A.G	Case 1 Mirza et al., 2004	Case 2 Mirza et al., 2004	Case 3 Mirza et al., 2004	Case 4 Mirza et al., 2004	Case 5 Mirza et al., 2004	Case 6 Mirza et al., 2004
Date of Birth	10/06/2017	08/11/1995	03/05/2000	13/01/1984	14/12/2000	02/04/2002	12/03/2000
Karyotype	46, XX, del (6) p25.3p24.3	46,XY,del(6) (p25.1)	46,XX, del(6)(p24)	46,XX,del (6) p25-pter	46,XX, del (6)(p24.3- pter):	46,XX,del(6) (p24.3)	46,XY,del (6) (p23p24.3) pter
Gender	Female	Male	Female	Female	Female	Female	Male
Developmental delay/ hypotonia	+	+	+	+	+	+	

(Continuação)

Table 1
(*continuação*)

	B.A.G	Case 1 Mirza et al., 2004	Case 2 Mirza et al., 2004	Case 3 Mirza et al., 2004	Case 4 Mirza et al., 2004	Case 5 Mirza et al., 2004	Case 6 Mirza et al., 2004
Abnormal skeleton	+				+		
Hydrocephalus	+			+			
Hypertelorism	+	+	+	+		+	+
Palpebral Fissure Defect		+		+			
Defects in the eye structure	+	+	+	+		+	+
Anomalies in the anterior chamber	+	+		+	+		
Abnormalities in the palate		+				+	+
Teething abnormalities		+	+	+			
Structural anomalies in the ears	+	+					+
Structural defects on the nose		+					+
Skin abnormalities							+
Marks on the skin		+					
Heart defects	+	+	+		+	+	+
Kidney Defects							+
Genital anomaly							+
Pectus Excavatum						+	+
Sensorineural hearing loss		+		+	+		
Imperforate anus							+
Neuronal Defect		+	+	+	+		
Motor Delay		+	+	+		+	
Anomalies in the fingers		+		+			+
Language delay		+	+				

Once analyzed the cases mentioned in Table 1, we observed a predominance of females over males, equivalent to 71.42% of all cases reported. The patient in this study is also female, which contributes to this high prevalence.

Delay in the neuropsychomotor development was reported in most cases (85,71%), including the patient in this study (B.A.G). By definition, neuropsychomotor development is a multidimensional and integral process closely related to the integrity and maturity of the central nervous system (CNS) and environmental interactions.

Structural and functional disorders from CNS may be influenced by genetic conditions.

Recent studies have led to the collection of phenotypic data for several rare diseases systematically. The mean odds of delay between the genetic groups were 8.3 times higher for sitting, 12.4 times for crawling, 26.8 times for walking, and 2.7 to 5.7 times for the language aspect²⁸ (WICKSTROM et al., 2021).

Another common finding in all the patients mentioned above is the increase of the distance between the eyes, with true lateral displacement of the orbits defined as hypertelorism. Hypertelorism is not a syndrome but a physical finding in many craniofacial syndromes, caused by an alteration in the embryological facial development

during the fourth and eighth week of intrauterine²⁹. Associated with this clinical finding, another manifestation very frequently in the analyzed phenotypes is defects in the ocular structure, which is present in six of the seven cases described, representing 85.71% of the patients reported, being the only patient who does not suffer from this condition is the Case 4. Also, there are anomalies in the anterior chamber, present in four of the seven patients mentioned above, including the patient in this study (BAG), equivalent to 57.14% of the total cases.

Concerning the cardiac defects, they are a relatively common abnormality when analyzing the patients with similar genotypic characteristics. Among the seven cases described, six have heart disease, which totalizes 85.71%, including the patient of this study (B.A.G). The only patient spared from these defects is the Case 3, whose karyotype is 46,XX, del (6) p35-pter.

Only two reported cases in Table 1 have skeleton abnormalities, namely: The patient of this study (B.A.G) and Case 4. In addition, both cases share cardiac defects, developmental delay, hypotonia, defects in the anterior chamber of the eye, and sensory hearing loss, and both are female. It is observed that the genetic deletion of both cases is found in similar parts of chromosome 6 (p24.3), which probably explains the phenotypic manifestation, but there is a need for further laboratory and cytogenetic investigation.

The other non-predominant phenotypic aspects were: hydrocephalus, which is present in only two cases described in the table above, the study patient (BAG) and Case 3. Both patients share deletions at the same locus on chromosome 6 (p25) and are female. Anomalies in the structure of the ears, which are present in three of the seven total cases described, represent 42.85% of the total number of patients mentioned above, including the patient reported in this study (BAG), case 1, and case 6.

In lower prevalence and not including the patient in the case (BAG), there are skin marks, present only in case number 1; abnormalities in the fingers, affecting only the patient in case 3; language delay, affecting only the patient in case 2; structural defects of the nose, present only in cases 1 and 6; anomalies in the palate,

observed only in cases 1, 5, and 6; dental abnormalities, only in cases 1, 2, and 3; renal defects, imperforate anus, and anomaly in the genitalia that affected only the patient in Case 6; pectus excavatum that affected only patients in Case 5 and 6 and sensory hearing loss presented only in Cases 1, 3, and 4.

The first case of a terminal deletion on chromosome 6 ever described was more precisely about deletion in 6p23 by Ouchi and Kasai (1982)³⁰. The clinical picture related by them referred to a newborn child with large anterior and posterior fontanelles, prominent occipital bone, hypoplasia of the lobe of the right ear, atresia of the right external auditory canal, apparently low ears, a left accessory lobe, cleft lip, cleft palate, micrognathia, short neck, excess skin nuchal, hypoplastic nipples, funnel chest, small external genitalia, clinodactyly of dewclaws and hypotonia, and later discovered a cardiac valvular abnormality.

Previous studies, such as that by Davies et al. (1999)¹³, revealed that syndromes caused by the deletion of part of chromosome 6p have similar clinical characteristics, such as Hypertelorism, congenital heart disease, ocular and skeletal disorders. Thus, the 6p deletion syndrome can then be divided into 1) deletions of 6p25 - which result in developmental defects, congenital heart defects, hearing and eye disorders, and craniofacial abnormalities such as hypertelorism, hypoplasia of the middle face, and ears with low implantation; 2) deletions of 6p22-24 that result in psychomotor retardation, renal malformation, short neck, a structural anomaly of the eyes, clinodactyly and syndactyly. The case studied and reported here includes modifications that resulted in craniofacial anomalies, hypertelorism, low implantation ears, and cardiac defects, and ophthalmic anomalies, thus having clinical manifestations of the two divisions of the 6p syndrome.

Reid and his collaborators (1983)¹¹ described a child with a deletion in the short arm of chromosome 6 (in 6p24.p25), who was born preterm with a 33-week GA, with hydrocephalus, Dandy-Walker cyst, clinical characteristics hypertelorism, corneal opacities, apparently low ears, pre-auricular mark, micrognathia, ectopic anus, and heart murmur. The picture previously described is very similar to that of the patient studied here, B.A.G.

New clinical pictures of deletions on chromosome 6 have been cited by Mirza et al. (2004)³¹ described, with karyotype 46, XY, del (6) (p25.1), hypertelorism, highlighting slightly low implantation of the ears, strabismus, cardiac defects, with changes in neuropsychomotor outcomes such as motor delay and difficulty in learning, and low to moderate sensorineural hearing loss.

At another point, the second patient described by Reid et al. (1983)¹¹, with a karyotype 46, XX, del (6) (p24), presented hypotonia at birth, and, later, his clinical picture became composed of hypertelorism, strabismus, bones, and heart problems. Also, the third patient analyzed, with a karyotype 46, XX, del (6) (p24.3-pter), had corneal opacity, heart defects, sensorineural hearing loss, and developmental delay in his clinical condition delays.

Considering the cases of the selected article, it is noted that the ocular abnormalities observed between the cases of terminal deletion described in G. A. B. and 6p are similar, which are compatible with the description of 6p terminal deletion syndrome. Other congenital issues such as heart defect, hydrocephalus, and defects in eye development are related to the *FOXC1* deletion³²⁻³³. Thus, the joint analysis corroborates the author's conclusion, pointing out that the clinical findings vary in the 6p interstitial deletion syndromes and include orofacial cleft, short neck, clinodactyly or syndactyly and brain, cardiac and renal defects. And associated with 6p terminal deletions, corneal opacity, iridogoniodysgenesis anomaly, various Rieger-type anomalies, hypertelorism, and deafness. These data are explained in Table 1 (above).

Establishing connections to other syndromes, there is clinical overlap in the patient presented with individuals who have the cranio-cerebello-cardiac syndrome (3C) (OMIM # 220210). In this sense, the clinical characteristics of the 3C syndrome, as discussed by DeScipio (2005)³⁴, include craniofacial anomalies, such as macrocephaly, prominent forehead and occipital, hypertelorism, downward sloping eyelid clefts, depressed nasal bridge, narrow or fissured palate, and low ears; cerebellar malformations, with variable manifestations of a Dandy-Walker formation with moderate cognitive retardation, and cardiac defects,

mainly septal defects, are very similar to the B.A.G phenotype.

When we first look at other syndromes and what these imply in the life of the patient and his family, we realize that adequate management is essential for multi-specialized teams, capable of serving not only the affected patient but also those who live with him since family dynamics are affected by the physical and/or mental limitations of the syndromic. It is in this context that special attention is prepared for such challenges, making family and team one time for a common good: providing health and development to a person affected genetically.

The relevance of the horizontal segment in childcare for adequate patient monitoring is also highlighted, with the deficiencies surrounding the case being identified to provide adequate referrals and therapeutic measures for the patient. It is important to emphasize the fundamentality of the multidisciplinary association with other professionals such as physiotherapists and speech therapists to promote a high quality of life for the patient and her family.

As for genetic counseling, it is important to note that B.A.G's parents were referred to the service. This communication process is carried out by a specialized and trained team that aims to guide an individual and/or their family about genetic diseases since about 80% of rare diseases are of genetic origin³⁵. Thus, genetic counseling is essential in caring for families and people with genetic diseases, as it includes not only the diagnosis but also the prognosis, possible management, heredity, and recurrence of the disease in other family members.

Thus, documenting clinical characteristics and comparing with findings in other reports in the literature is of great relevance as it allows for a better diagnosis and an accurate prognosis for patients with suspected similar chromosomal deletions³⁴.

CONCLUSION

The syndrome of terminal deletion on chromosome 6, including the deletion of a terminal segment deletion of 8,9 Mb on the short arm of chromosome 6 (in 6p25.3p24.3), is associated

with a large phenotypic spectrum with varied clinical findings, in which the presence of hyper-telorism, anomalies in the anterior chamber of the eye, hearing loss, and developmental delay are highlighted. In this sense, the organization of a multidisciplinary team capable of suspecting and subsequently diagnosing the cytogenetic anomaly, as well as monitoring the patient's development, is essential to achieve the best possible prognosis. In addition, genetic counseling should be indicated to observe cases of heredity or recurrence in other family members.

Thus, with the permanence of the condition's rarity, the practice of national and international records is of great importance, with systematic and prospective data collection to better document the incidence, modes of presentation, current treatment practices, complications, and prognosis of the syndrome. Furthermore, the importance of documentation through scientific writing is indisputable as case reports to assist and increase the index of clinical suspicion in health networks, especially in the field of public health, increasing the understanding between the genotype-phenotype correlation and fostering the possibility of differential diagnoses for clinical cases with similar presentations.

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Contribuição dos autores:

BZS: Escreveu resumo, introdução, objetivos, metodologia, resultados, discussão e conclusão. Também realizou a pesquisa de referências, conversou com os responsáveis pela paciente e fez registro dos exames laboratoriais e laudos.

LBZ: Escreveu a descrição do caso, discussão e conclusão, também realizou a tradução do artigo para o inglês.

EMC: Professora que introduziu o caso da paciente às autoras e guiou e orientou a escrita do artigo.

CTA: Professora que orientou a escrita do artigo.

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