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Andes pediatr. 2024;95(6):771-777
DOI: 10.32641/andespediatr.v95i6.5094

CLINICAL CASE

# Warsaw syndrome: a cohesinopathy as etiology of primary microcephaly

## Síndrome de Varsovia: una cohesinopatía como etiología de microcefalia primaria

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Received: January 9, 2024; Approved: Jul 4, 2024

**What do we know about the subject matter of this study?**

The description of genetic causes of microcephaly has recently gained relevance. Advances in molecular study techniques have made it possible to describe new entities. Warsaw breakage syndrome is a rare genetic condition that manifests with severe microcephaly.

**What does this study contribute to what is already known?**

This case report describes the diagnostic process and management of this rare condition. The usefulness of evaluation by a geneticist and the diagnostic role of whole exome sequencing in these cases are highlighted. The limited genotypic and phenotypic knowledge of the Latin American population is expanded.

## Abstract

Warsaw Breakage Syndrome (WABS) is a very rare autosomal recessive disease. To date, only 24 cases have been described in medical literature. There are descriptions of patients from various ethnic origins, but only one of them is from Latin America, in Uruguay. **Objective:** to report a clinical case from Chile, which presented the classic triad, in order to characterize its phenotype and contribute to the description in Latin America of this syndrome. **Clinical Case:** Male patient, second child of consanguineous parents. Pregnancy with intrauterine growth restriction, born preterm at 33 weeks of gestational age, head circumference 24 centimeters (-5 to -6 SD); infectious and metabolic evaluation were normal. Brain MRI without relevant pathological findings. He has left deafness and severe hearing loss in his right ear, using a cochlear implant in the left ear. Head circumference remains always close to -6SD, length and weight below -2SD. Considering the triad of deafness, microcephaly, and growth restriction, whole exome sequencing was performed, finding a homozygous variant likely pathogenic in the *DDX11* gene. **Conclusions:** The knowledge about this syndrome allows clinical suspicion and,

**Keywords:**
Microcephaly;
Exome Sequencing;
Fetal Growth Retardation;
DNA Repair-Deficiency Disorders;
Childhood Developmental Disorders;
Hearing Loss;
Warsaw Syndrome

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Edited by:
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How to cite this article: Andes pediatr. 2024;95(6):771-777. DOI: 10.32641/andespediatr.v95i6.5094

thus, to perform an early genetic study that allows confirming or ruling out the diagnosis, providing adequate genetic counseling, and having a correct prognosis estimation. Medical literature on this is limited and does not allow us to make exact estimates on the evolution of each patient, however, the report of new cases such as ours, contributes to the knowledge and management of other patients with the syndrome.

## Introduction

Warsaw Breakage Syndrome (WABS; OMIM #613398) is a very rare autosomal recessive disease due to pathogenic variants in the gene encoding DNA helicase *DDX11*[1,2]. In 2010, a male patient with a heterozygous variant in the *DDX11* gene was described, with clinical characteristics similar to Fanconi anemia, but without bone marrow failure[3,4]. To date, 24 cases of this syndrome have been identified in the literature. There are descriptions of patients with different ethnic origins, but only one of them is Latin American, from Uruguay[1].

WABS belongs to the group of cohesinopathies, which are pathologies caused by pathogenic variants in genes encoding subunits of the cohesin complex or proteins with regulatory roles in the process of sister chromatid cohesion; Cornelia de Lange syndrome and Roberts syndrome are also recognized within this group[1,5]. Clinically, it is characterized by the triad of pre- and post-natal growth restriction, severe pre- and post-natal microcephaly, and sensorineural hearing loss with cochlear alterations, which was present in all the patients described. Other frequent manifestations are intellectual disability and facial dysmorphia. In addition, skeletal and heart abnormalities, hypotonia, recurrent infections, skin pigmentation alterations (hyper- and hypopigmented macules, cutis marmorata, livedo reticularis, and telangiectasias), and genitourinary anomalies may be observed[1,5,6].

We report a case in Chile that manifested with the classic triad, identifying a probably pathogenic homozygous variant in the *DDX11* gene, to characterize its phenotype and contribute to the description of the syndrome in Latin America.

## Clinical Case

Male patient, the second child of consanguineous young parents (first cousins). He has a healthy 6-year-old brother with normal development. During pregnancy, the mother was hospitalized due to oligohydramnios secondary to premature rupture of membranes at 13 weeks of gestation, in addition to intrauterine growth restriction. He received corticosteroid maturation two times. No infections were evidenced during pregnancy.

The patient was born preterm at 33 weeks gestational age (GA), birth weight 1,330 grams (-3 SD), head circumference 24 centimeters (-5 SD), and length 40 centimeters (-1 SD)[7]. He remained hospitalized for approximately 30 days under study for microcephaly, with infectious and metabolic studies, including screening for cytomegalovirus, phenylketonuria, and hypothyroidism, all of which were negative. Skull X-rays and CT scans showed patent sutures. Neonatal transfontanelar brain ultrasound reported a grade II germinal matrix hemorrhage, which was confirmed with brain MRI, which also showed a lower degree of myelination than expected for gestational age, with no other relevant pathological findings. A new brain MRI at 8 months of age showed severe dilation of the ventricular trigone and the left occipital and temporal horns, with no evidence of transependymal edema.

A fundus examination, echocardiogram, and abdominal ultrasound were performed, which ruled out pathological findings. The auditory study during the neonatal period showed bilateral alteration in the brainstem auditory evoked potentials (BAEP). At 21 months of corrected age, a left cochlear implant was placed, however, in the last check-up, there was complete deafness in the left ear and hearing loss in the right ear.

At one year of age, he was evaluated by a clinical geneticist, highlighting on physical examination anthropometry with lower length and weight than expected at that age (< -2 SD), and severe microcephaly, with a head circumference of -6.6 SD. At the age of 3, he persists with severe microcephaly, with a head circumference of 39.5 cm (-6 SD)[8].

From a dysmorphic perspective, the following were identified: upslanting palpebral fissures, epicanthus inversus, low nasal bridge, wide nasal base, short columella, cryptorchidism of the right teste, *café-au-lait* spots on the right leg and hyperpigmented spots at the scapular level, bilateral clinodactyly of the 5th fingers, and overlapping toes on both feet (Figure 1).

The genetic study began with a karyotype in lymphocytes (46,XY). Given the triad of hearing loss, microcephaly, and growth restriction, a whole exome sequencing was performed, revealing a likely

pathogenic homozygous variant in the *DDX11* gene (NM_030653.3:c.1403dup,p.(Ser469Valfs*32)). As a result of these variants, two truncated proteins are produced that fail to form a functional *DDX11* helicase. The loss of function of this protein is recognized as the causative mechanism of WABS. This gene is a member of the superfamily 2 (SF2) of helicases and contains iron-sulfur (FeS) and a DEAD/DEAH box. These helicases are vital for genomic stability and maintenance. Therefore, the main role of the *DDX11* gene is related to the latter and is involved in sister chromatid cohesion, DNA repair, and the normal chromatin structure. Its alteration generates an increase in chromosomal breakage[6].

Among the gross psychomotor development milestones, the following stand out: the patient began to walk at 17 months of corrected age, managing to run and jump at 3 years of age; in fine motor development, at the age of 3, he made pencil lines and uses a spoon to eat; in language development, he said his first words at 2 years of age, and by age 3, he could say approximately 5 words; in social development, he managed to imitate actions at 3 years of age, understands "no", responds to his name, and recognizes himself in the mirror, although he still does not achieve joint attention, symbolic play, or recognize parts of his body.

In the 3-year evaluation, bilateral lower extremity spasticity with clubfoot associated with contracture of both Achilles tendons was reported, for which he uses day and night orthosis as indicated by physiatrists. In addition, he reports emotional dysregulation events with heteroaggressions and marked hyperactivity that require management with Risperidone to optimize his stimulation therapies.

## Discussion

The first description of WABS was made in 2010 by van der Lelij in a male patient with severe intrauterine growth restriction and microcephaly associated with facial dysmorphias (small and long face, narrow bifrontal diameter, bilateral epicanthal fold, relatively large mouth, and cup-shaped ears), clinodactyly of the 5th fingers, syndactyly of the second and third toes, abnormal skin pigmentation, and hearing loss due to cochlear hypoplasia; with psychomotor and mental development described as mildly delayed[4,9].

WABS is now recognized as a syndrome with a heterogeneous spectrum of manifestations, although some are characteristic. The triad of pre- and post-natal growth delay, severe microcephaly, and sensorineural hearing loss associated with cochlear and cochlear nerve hypoplasia represent the cardinal features of the syndrome. Facial dysmorphia, clinodactyly, and skin pigmentation alterations are present in most cases. The other manifestations described, such as heart and genitourinary symptoms, are recognized in fewer cases[1,10,11]. Within the neurological spectrum, structural brain abnormalities such as focal simplification of the gyral pattern and lissencephaly have been described, as well as epileptic seizures[6,11]. The facial dysmorphisms described include a sloping forehead, prominent eyes with upslanting palpebral fissures, epicanthus, and broad nasal bridge, with small nostrils and mouth[5]. Table 1 summarizes the main features published to date. It is important to mention that the spasticity of the case described could also be explained by his prematurity and may not necessarily be due to his genetic condition.

The maintenance of genome stability and its proper propagation are key points in proper cell development and proliferation. In this sense, the cohesin pathway is a point of convergence of several biological processes: sister chromatid cohesion, genome organization, regulation of gene expression, DNA repair, and genome protection. Cohesinopathies are a group of conditions in which genomic instability is generated, manifested as chromosomal aberrations, early centromeric division, early sister chromatid separation, and sensitivity to genotoxic drugs, among others. The *DDX11* gene acts as a regulator and is important for functional coupling between DNA synthesis and the establishment of cohesion at replication forks[1,3,5,12]. Cohesion defects are observed in metaphase chromosomes in WABS, with a characteristic "railroad" configuration of sister chromatids with a lax centromeric constriction[10,13,14].

Studies have shown that affected individuals with conditions associated with chromosomal instability would have increased DNA breakage in the presence of compounds such as mitomycin C, diepoxybutane, and cisplatin[6,11,14,15]. Its etiopathogenesis is not well known, mainly due to the absence of animal models of the disease, since the knockout mouse model presents embryonic lethality, which leads to a limited knowledge of the cellular functions of *DDX11*[1].

The syndrome has variable expressions and overlaps clinically with other chromosomal breakage syndromes. One of the important differential diagnoses is Fanconi anemia, another autosomal recessive chromosomal instability syndrome characterized by several manifestations including the cardinal symptoms of WABS but associated with progressive bone marrow failure and a marked predisposition to cancer. In addition, we should consider the Nijmegen breakage syndrome, which is differentiated by its severe immunodeficiency phenotype. Although the *DDX11* gene may act as a tumor suppressor, cancer has not been described in any reported patient.

So far, the oldest published case of WABS died at

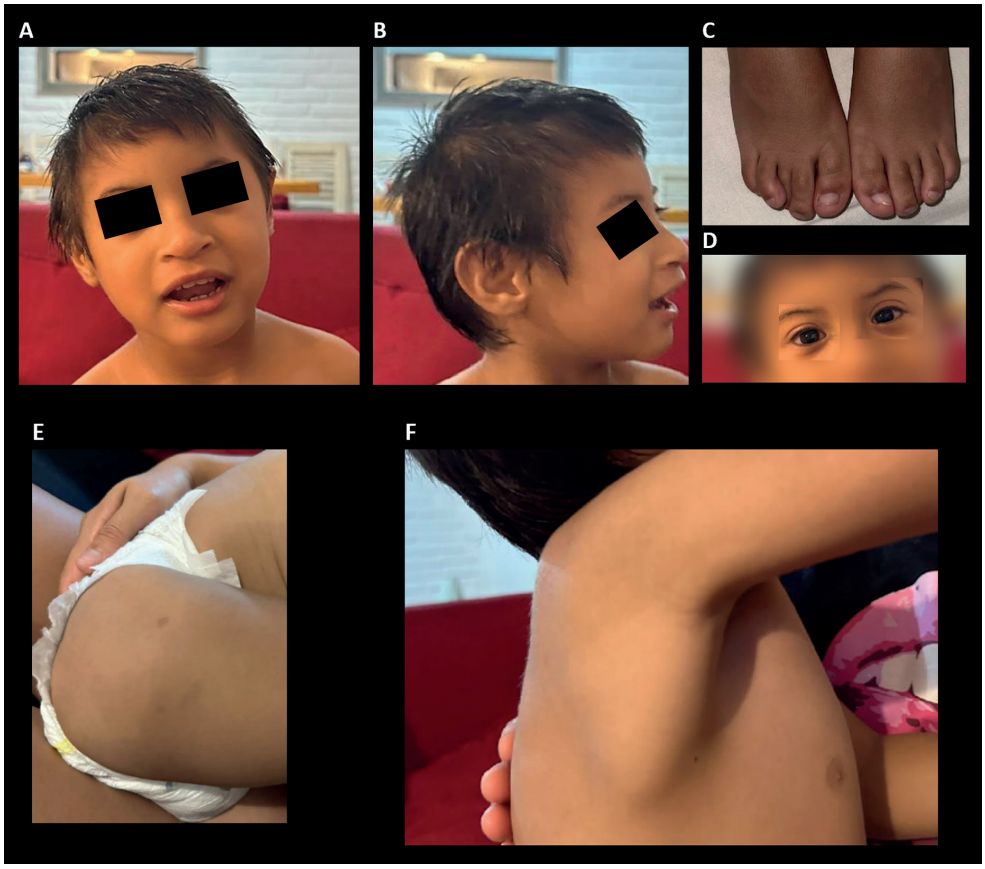


**Figure 1.** Physical manifestations in a Chilean patient with WABS. A: low nasal bridge, wide nasal base with horizontalized nostrils, short columella and thin upper lip. B: long ear. C: overlapping toes on both feet. D: upslanting palpebral fissures, tendency toward epicanthus inversus. E and F: Pigmentary skin alterations. Hyper- and hypopigmented macules on legs and arms. Sharp, irregular borders, without distribution along Blaschko lines.

64 years of age without evidence of cancer, therefore, in the absence of established risk of cancer in carriers, there are no guidelines for early follow-up or risk indicators. Other important cohesinopathies are Cornelia de Lange and Roberts syndrome, which are differentiated by the shortening of the extremities[1,3,6,13,14]. Finally, it should be recognized as a possible differential diagnosis of Microcephalic Osteodysplastic Primordial Dwarfism type II, which shares microcephaly and short stature, but also presents bone or dental alterations, vascular alterations of the CNS, and, in general, a more severe short stature[16].

The WABS should be suspected from the neonatal period in a patient with intrauterine growth restriction and severe microcephaly after other non-genetic etiologic causes, especially if there is hearing compromise and a history of consanguinity between the parents. It is important to ensure that the genetic diagnostic strategy targeting causative genes for congenital microcephaly includes the *DDX11* gene.[1]. If the diagnosis is confirmed, we recommend maintaining follow-up by a multidisciplinary team that includes pediatric neurologists, otorhinolaryngologists, geneticists, traumatologists and orthopedics, physiatrists, and physical, speech, and occupational therapy.

Genetic counseling provides patients and their families with information that helps them to make decisions regarding family planning and to learn about options to reduce the risk of transmission (gamete donation, preimplantation genetic testing, and adoption, among others). Being an autosomal recessive inherited disease, the risk of recurrence is 25% in each future pregnancy of the same couple. Without studying the parents, we can assume that they are heterozygous carriers of the causal variant, which allows us to establish specific family planning strategies.

As reported in the literature to date, our patient presented the classic triad detected in the neonatal period. The importance of knowing this syndrome is emphasized in order to maintain a high level of clinical suspicion, and thus, to perform the corresponding genetic study early to provide adequate genetic counsel-

**Table 1. Phenotypic characteristics most frequently observed in patients with WABS. Adapted from van Schie, J et al. (2020)(3) y Pisani, F. (2019)[14]**

| Phenotype \ Reference | Van der Lelij et al (2010) (N = 1)[9] | | Capo-Chichi et al (2013) (N = 3)[17] | | | Bailey et al (2015) (N = 1)[4] | Eppley et al (2017) (N = 2)[5] | | Alkhunaizi et al (2018) (N = 5)[11] | | | | | Bottega et al (2019) (N = 2)[18] | | Rabin et al (2019) (N = 2)[6] | | Van Schie et al (2020) (N = 7)[3] | | | | | | Arroyo-Carrera et al (2023)[1] | Caso presentado | Total de pacientes (N = 25) | Proportion as a percentage of the total cases with available report |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Sex | M | F | M | M | F | F | F | F | M | M | F | M | M | F | F | M | F | M | M | F | M | M | M | M | 14 M<br>11 F | 56%<br>44% |
| Consanguinity | - | + | + | + | + | - | - | - | - | + | + | + | + | + | - | - | - | - | - | - | - | - | - | + | + (8)<br>- (17) | 32% |
| Intrauterine growth restriction | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | ND | + | + | + | + | + | + | + | + | + (22)<br>- (1)<br>ND (2) | 96% |
| Post-natal growth retardation | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + (22)<br>- (1)<br>ND (2) | 96% |
| Microcephaly | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + (25) | 100% |
| Intellectual disability | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + (21)<br>- (1)<br>ND (3) | 95% |
| Facial dysmorphia | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + (25) | 100% |
| Skeletal abnormalities of fingers/toes | + | + | + | - | + | + | + | + | + | + | + | + | + | + | ND | + | + | + | ND | ND | ND | ND | ND | - | + (14)<br>- (3)<br>ND (8) | 82% |
| Congenital hearing loss | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + (23)<br>ND (2) | 100% |
| Heart abnormalities | + | - | + | + | - | + | ND | ND | + | - | + | + | - | ND | ND | - | + | + | ND | ND | ND | ND | ND | + | + (7)<br>- (7)<br>ND (11) | 50% |
| Brain abnormalities | ND | ND | ND | ND | ND | ND | ND | ND | + | + | ND | + | + | ND | ND | ND | + | + | - | ND | + | + | ND | - | + (9)<br>- (2)<br>ND (14) | 82% |
| Seizures (epilepsy) | ND | ND | ND | ND | ND | - | - | - | + | + | ND | + | + | ND | ND | + | + | + | + | + | ND | ND | ND | + | + (6)<br>- (4)<br>ND (15) | 60% |

Abbreviations. N: Number; M: Male; F: Female; NA: Not Available

ing and to have a correct estimation of the short- and long-term prognosis. The literature on this subject is limited and does not allow us to make exact estimates on the progression of each patient; however, the report of new cases such as ours contributes to the knowledge and management of patients with the syndrome.

## Ethical Responsibilities

**Human Beings and animals protection:** Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

**Data confidentiality:** The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

**Rights to privacy and informed consent:** The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

## Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

## Financial Disclosure

Authors state that no economic support has been associated with the present study.

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