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CASE REPORT OPEN ACCESS

ROBINOW SYNDROME: A CASE REPORT

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ABSTRACT

This paper proposes to describe the case of a 25-year-old female patient, affected by Robinow Syndrome type 2, who was treated at the Medical Specialties Center of the University Center of the State of Pará (CEMEC, CESUPA). A case report increases scientific knowledge about, in this case, a rare disease, which may present difficulties in the diagnostic and treatment for someone who has not been introduced to the subject, generating clinical error and ineffective treatment. The patient had a molecular test for skeletal dysplasia with alteration in the DVL1 gene, confirming the diagnosis of Robinow Syndrome type 2. Notes of her consultations were taken in the following specialties: genetics, orthopedics, gynecology, nephrology, neurology and hematology, including the dates and conduct of each appointment. The patient remains, above all, hopeful about the future of her treatment, although she recognizes that a possible heart condition could lead her to death. She has no problem accepting her disability status. What bothers her most is the migraines, which causes serious functional impairment and for which treatment is generally ineffective.

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INTRODUCTION

Patient E. S. P., female, born on January 29, 1998, currently 25 years old, from Belém (PA), with a birthplace in Bragança (PA). Marital status: single, residing in the Tapanã neighborhood, Belém. Currently a student. Sedentary, maintaining a standard diet with no restrictions. Regarding her previous diagnoses: Robinow Syndrome; hypophosphatasia; recurrent urinary tract infection; chronic kidney disease; migraines; abnormal uterine bleeding; and bicornuate uterus. In terms of anthropometric indices, she is 137 centimeters tall and weighs around 40 kilograms. As for personal history, the patient denies smoking, alcohol consumption, use of legal or illegal drugs, medication or food allergies, traumas, or previous accidents. However, in 2019, during a neurology outpatient visit, the patient mentioned being hospitalized in childhood due to dyspnea and, in 2009, experiencing a motorcycle accident with a cranial vault fracture. She denies self-esteem and acceptance issues related to her disability. Mental health problems, such as depression with suicidal ideation, were attributed to external factors, such as the use of Topiramate 50mg and interpersonal relationships. Up to the age of 8, she underwent 8 orofacial surgeries, including gingivoplasty, extractions of malformed teeth, and tongue reconstruction. At the age of 15, she underwent umbilical hernioplasty. Concerning her family history, her siblings also have hypophosphatasia due to both parents carrying the gene for this condition. Maternal grandmother with bronchopulmonary neoplasia. She is the first family member with Robinow Syndrome.

MATERIALS AND METHODS

Descriptive, individualized, narrative, observational, cross-sectional study. Conducted through the analysis of the medical record of a patient with Robinow Syndrome. The research was carried out through the collection and analysis of data obtained from the medical record of a patient treated at the Center for Medical Specialties (CEMEC) of the State University Center of Pará (CESUPA), located at Avenida Almirante Barroso, number 3775 in Belém, Pará. The research and data collection were conducted in February and March 2022. Having agreed to participate in the study, the patient signed the Informed Consent Form (ICF), and their analyzed data were used for analysis and included in the research protocol. The patient was studied according to the principles of the Helsinki Declaration, the Nuremberg Code, and respecting the Standards for Research Involving Human Beings (CNS Resolution 466/12), of the National Health Council. The research was carried out after project approval by the Research Ethics Committee with human subjects at the State University Center of Pará. Data collection took place after the signing

of the Data Utilization Commitment Agreement (DUCD), Informed Consent Form (ICF), and Acceptance from the Educational Institution.

RESULTS

The patient registered for consultation at the Genetics Outpatient Clinic of the Clinical Specialties Center at the State University Center of Pará (CEMEC - CESUPA) on October 5, 2017. At the time, the 19-year-old patient reported having a sister under investigation for bone fragility and suspected hypophosphatasia (HPP) due to an extensive fracture after a fall from her own height and laboratory findings of alkaline phosphatase below the reference value. On December 11, 2017, she underwent a molecular test for skeletal dysplasias with a mutation in the ALPL gene, confirming the presence of hypophosphatasia, as well as a mutation in the DVL1 gene, confirming a diagnosis of Robinow Syndrome type 2, as per the examination transcript below.

The test the patient underwent was a molecular study for skeletal dysplasias. She was referred to this test to clarify the diagnosis of Robinow syndrome, which was suggestive until then. Additionally, the patient had tooth loss and a family history of hypophosphatasia (her sister has the disease). Results: Pathogenic alterations were identified in the ALPL and DVL1 genes. Interpretation: Regarding the alterations c.1363G>A (p.Gly455Ser) and c.1426G>A (p.Glu476Lys), located in exon 12 of the ALPL gene: previously described in patients with clinical hypophosphatasia; they are in trans, confirming distinct parental origins. Concerning the variant c.1496_1508del (p.Pro499Argfs*146), detected in exon 14 of the DVL1 gene: previously reported in an individual with a suspected diagnosis of Robinow syndrome. Given this information and following the guidelines defined by the American College of Medical Genetics and Genomics (ACMG), the above result is consistent with the clinical presentation of the patient.

As detailed below, the patient has been attended by physicians from various specialties, including geneticists, orthopedists, gynecologists, neurologists, nephrologists, endocrinologists, and hematologists. The prescribed medications from the latest reported consultations include: Colecalciferol and Neutrofer, prescribed in 2021.Injectable Depo-Provera every 3 months (replacing Desogestrel) and Trok for xerotic lesions, both prescribed in May 2022.Enalapril 2.5mg, which the patient should take but faced financial difficulties in acquiring the medication.Noripurum is also being used. The patient has struggled significantly with persistent frontal headaches. After multiple consultations in the neurology outpatient clinic, with adjustments in dosage and the prescription of new medications, the patient ended up with a prescription for Dipirona 500mg every 12 hours, Propranolol 40mg, and Topiramate 25mg at night. However, she does not believe in the efficacy of these medications and reports no improvement in symptoms, even after trying different dosages and various drugs. Presentation by Specialty and Chronology of Relevant Consultations for the Description of Robinow Syndrome Case. Other consultations of little relevance to the genetic disease description have been omitted.

Genetics: 05/10/2017: First consultation at the Center for Medical Specialties (CEMEC). The patient, then 19 years old, reported having a sister undergoing investigation for bone fragility and suspected hypophosphatasia (HPP), given a low alkaline phosphatase level. Course of action: whole-body X-ray, alkaline phosphatase, and vitamin B6. Follow-up consultation. Complaints of pain in both knees, leg pain when climbing stairs, and intense frontal headache. Molecular examination for skeletal dysplasias (requested on 11/12/2017, delivered on 27/03/2018): alteration in the ALPL gene confirms the presence of hypophosphatasia; alteration in the DVL1 gene confirms the diagnosis of Robinow syndrome type 2. Course of action: referral to the orthopedist, ophthalmologist, otorhinolaryngologist, and gynecologist. 04/04/2019: Complaints of pain. Reported recurrent urinary tract infection, arthralgia, and ring fingers of both hands with a change in color to a purplish appearance. Course of action: prescription of Ciprofloxacin 500mg every 12 hours for 7 days, and referral to the neurologist and nephrologist. 03/10/2019: Complaint of pain in the lower limbs. The patient presented some exams. Total abdominal ultrasound: the right kidney with preserved dimensions, apparently with axis rotation with inversion/lateralization of the pelvis, and increased cortical echogenicity; the left kidney not characterized. Ultrasound of the kidney and urinary tract: the right kidney with normal dimensions, showing retraction in the middle third of scar-like appearance, and also a bad rotation of this same kidney; the left kidney has reduced dimensions, with thinning of the renal parenchyma, showing retraction in the middle third of probable scar-like nature and also presenting bad rotation of this left kidney. Ultrasound of both feet: a hypothesis of osteodegenerative changes in the joint, characterized by osteophytic reaction on the articular surfaces, especially in the right foot. Transthoracic ultrasound: no changes. Course of action: Ketoconazole and referral to the otorhinolaryngologist and ophthalmologist.

Orthopedics: 27/02/2019: Patient then 21 years old; reported pain in the lower limbs since childhood that had been intensifying over time; had intense pain in the right foot accompanied by swelling and a change in skin color to purple, in addition to difficulty walking. Went to the Emergency Care Unit (UPA) but did not recall the medication that had been prescribed. Physical examination: Patrick's test bilaterally. Flattening of the arches and shortening of the toes; feet deviated to the sides. Course of action: request for ultrasound of both feet, X-ray of the pelvis, and feet. This ultrasound of both feet was presented at the genetics outpatient clinic on 03/10/2019.

Gynecology: 21/05/2019: Patient complaint regarding contraceptive method and increased menstrual flow. Menarche occurred around the age of 14. Asymmetric breasts with no other alterations. Vulva is typically feminine. Course of action: total abdominal ultrasound, transvaginal ultrasound, and coagulogram.

17/12/2019: Complaint of increased uterine bleeding. Exam results: transvaginal ultrasound (05/08/2019): showed the uterus in anteverted position, bilobed (bicornuate), with a volume of 63cm3, and additionally, the bipartite heterogeneous endometrium in the upper third. Course of action: Desogestrel (continuous use oral contraceptive).

02/02/2021: The patient stopped taking Desogestrel on her own after reading the drug's leaflet and discovering its drug interaction with Topiramate, which she was already taking at a dose of 25mg, one capsule at night. Pap smear (02/02/2021): no changes. Course of action: patient referred to the nephrologist and endocrine gynecologist.

25/05/2021 (endocrine gynecologist): Patient complaint of abnormal uterine bleeding, hypermenorrhea, and irregular cycles. The patient reiterated her reason for discontinuing the use of oral contraceptive (OC). Course of action: advised to follow up at the outpatient clinic and recommended to record her menstrual cycles.

22/06/2021 (gynecologist): The patient brought requested exams. Menstruation is regular, with normal flow and duration. Transvaginal ultrasound (13/05/2021): uterus in anteverted position (AVF), bilobed, with thin walls, compatible with bicornuate uterus, measuring 5.6cm x 2.8cm x 5.0cm, with a volume of 35.1cm3; echogenic, bilaminar endometrium, bipartite in the upper third, measuring 3mm thick on the right and 2.2mm on the left; right ovary volume 1.6cm3, left volume 0.4cm3; ultrasound suggests Mullerian malformation compatible with bicornuate uterus. Hemogram (19/05/2021): urea 18, creatinine 0.34. Course of action: return to the consultation with tests, namely total cholesterol, HDL, LDL, urine, and hemogram.

18/05/2022: Evaluation of hypermenorrhea at the request of the hematologist, with the patient needing to enter amenorrhea for at least 6 months. Course of action: prescription of injectable Depo-Provera

every 3 months, Trok for xerotic lesions, and request for transvaginal ultrasound (USGTV).

Nephrology: 24/04/2019: Recurrent urinary tract infection (UTI) since childhood, occurring mainly after the menstrual period, with dysuria, lower abdominal pain, chills, and high fever (39ºC to 40ºC). Bilateral renal pain, yellowish malodorous leukorrhea. The patient also reported stress urinary incontinence. In the Inquiry about Various Systems (ISDA), she presented constant migraines. Complementary exams (16/09/2017): static renal scintigraphy (DMSA):Left Kidney: 19.84%Right Kidney: 80.16%. Dynamic renal scintigraphy (DTPA): Left Kidney: 19.6%Right Kidney: 80.4%. And renal function:Left Kidney = 7.956 mL/Min Right Kidney = 38.7 mL/Min.

The diagnostic hypothesis (HD) was chronic kidney disease (CKD) due to anatomical alteration, in addition to recurrent urinary tract infection (Recurrent UTI). Course of action: request for urine culture with antibiogram, static renal scintigraphy, and ultrasound of the kidneys and urinary tract.

25/05/2021: Follow-up for CKD and recurrent UTI. Course of action: static renal scintigraphy, ultrasound of the kidneys and urinary tract.

08/09/2021: No UTI since the last appointment, but intermittent dysuria and recurrent lumbalgia. ISDA: 2 doses of Pfizer vaccine. Course of action: prescription of Colecalciferol and Neutrofer, patient referred to endocrinologist and mental health. Possibly affected by primary dyslipidemia.

23/03/2022: Patient took a new dose of the Pfizer vaccine, completing 3 doses. Presented exams. Hemogram from 09/02/22:

Hb: 9.9 | Ht: 30 | RBC: 4.21 | MCV: 77.4 | MCH: 23.5 | Leukocytes: 8900 | Platelets: 300000 | ESR: 50 | Vitamin D: 64 | Glucose: 102 | Uric Acid: 4.7 | TC: 247 | HDL: 39 | LDL: 145 | TG: 314 | Urea: 14 | Creatinine: 0.64 | Serum Iron: 76 | Calcium: 10.1 | Sodium: 141 | Phosphorus: 4.4 | Potassium: 3.8 | Ferritin: 144 | Isolated Microalbuminuria: 54 | Abnormal Sediment Elements (ASE) (urine test): frequent epithelial cells, 4-6 pyocytes, frequent mucus filaments, frequent bacterial flora.

Static renal scintigraphy (DMSA) (16/09/2021): typical kidneys; left kidney reduced in size and hypoconcentrated tracer compared to the contralateral; both kidneys with heterogeneous tracer distribution, showing irregular cortical contour. Absolute quantification: left kidney 9%, right kidney 23%. Relative quantification: left kidney 28%, right kidney 72%. Impression: bilaterally decreased tubular function, markedly on the left; presence of images of cortical contour retractions, possibly related to scars. Diagnostic hypothesis (HD): stage 1 chronic kidney disease (CKD) (structural); mixed dyslipidemia; anemia to be clarified; chronic pain related to hypophosphatemia. Course of action: Enalapril 2.5 (due to microalbuminuria of 54mg/g) and Ciprofibrate 100mg. Request for complete iron profile, B12 and folate dosage, isolated microalbuminuria, complete blood count, lipid and renal profile. Referral to hematology for evaluation of chronic anemia (not related to CKD due to this disease still being in the initial stage).

27/04/2022: The patient did not adhere to Ciprofibrate 100mg due to financial difficulties and stopped Enalapril 2.5mg after episodes of dizziness. Bilateral lumbalgia persists, especially on the left side. Course of action: request for complete iron profile, B12 and folate dosage, isolated microalbuminuria, complete blood count, lipid and renal profile, along with a new prescription for Enalapril 2.5mg, this time to be used at night.

21/09/2022: The patient could not perform the previously prescribed exams. Reported improvement in bilateral lumbalgia. Denied dysuria, polyacrylate, polyuria, and fever. Reported polyphagia, polydipsia, and disposition after using Noripurum (this medication was prescribed in the Neurology and Hematology specialties). ISDA: pain in the right femur, palpitations, and "burning" on the tongue. Course of action: request for uric acid, total and fractionated cholesterol, urea, creatinine, glucose, glycated hemoglobin, total and fractionated proteins, triglycerides, sodium, potassium, calcium, iron, ferritin, and transferrin.

Neurology: 21/05/2019: Three years ago, the patient presented pulsatile headache throughout the entire head, radiating to the neck, one to two times per week, associated with photophobia. One year prior to the consultation date, it progressed to a daily condition, and the patient used Neosaldina. ISDA: mouth breathing, polyuria, dysuria, resting tachycardia, and insomnia. Personal history: irregular menstruation, metrorrhagia, umbilical and palate and gum hernia surgery; the patient was also hospitalized in childhood for dyspnea and had a motorcycle accident 10 years before the consultation date, with a cranial vault fracture; furthermore, postpartum hydrocephalus without the need for surgery. Diagnostic hypothesis (HD): migraine without aura. Course of action: request for contrast-free cranial magnetic resonance imaging, echocardiogram, and electrocardiogram; prescription of Propranolol 40mg.

03/09/2019: About three months later, the patient reported improvement in pain and palpitations but with insomnia. Course of action: additional prescription of Amato (Topiramate).

21/07/2020: Patient reports significant improvement in pain and palpitations. Course of action: request for a cranial magnetic resonance imaging.

21/10/2020: After three months of treatment, the patient returned reporting the same headache pattern. Course of action: increased dose of Amato, from 25mg to 50mg, discontinuation of the prescription for Propranolol 40mg.

23/12/2020 (cranial magnetic resonance imaging): Macrocephaly, with discreet foci of gliosis consistent with the headache condition, hypertelorism, and enlarged cisterna magna. Course of action: the same medications were maintained.

09/03/2021: The patient returned to neurology with a worsening headache, loss of appetite, and depressive symptoms associated with an increase in the Amato dose. The patient independently reduced the dose from 50mg to 25mg, leading to symptom improvement. She also reported nausea, photophobia, phonophobia, and dizziness. Examination findings included a third heart sound (S3) during cardiac auscultation. Hemogram results on 09/02/2021 indicated:

Hb: 10.7 | Ht: 32.7 | RBC: 4.42 | MCV: 74 | MCH: 24.2 | MCHC: 32.7 |
Leukocytes: 15,010 | Platelets: 38,800 | Urea: 35 | Creatinine: 0.8 | Glucose: 96
| Sodium: 139 | Potassium: 4.5 | Total Cholesterol: 229 | LDL: 158 | HDL: 58 | Urine: density 1020, pH 6, 3 pyocytes, frequent epithelial cells, without other changes.

Diagnostic hypothesis (DH): Iron-deficiency anemia to be clarified. The approach was to maintain Topiramate 25mg and prescribe a new Propranolol 40mg, half a tablet per day. Follow-up in 4 months.

15/06/2021: The patient presented with the same intense headache, accompanied by nausea. The approach was to administer Propranolol half a capsule twice a day and maintain Amato 25mg.

26/10/2021: Reported daily headache, accompanied by nausea and phonophobia; the patient took Paracetamol every day; insomnia. The approach included Vertix 10mg, one capsule for 60 days, Noripurum chewable one capsule before lunch and another before dinner; referral to cardiology.

22/01/2022: No improvement in the headache. The approach involved maintaining the prescription of Amato 25mg, one tablet at night; discontinuing the use of Propranolol and Paracetamol; adding Amplictil 4%, four drops every eight hours in case of pain.

08/02/2022: Headache persisted. The approach was to use Flanax every 12 hours if there is pain; everything else was maintained.

08/03/2022: The patient reported using Naproxen in two episodes of pain for 3 weeks, with improvement in symptoms. She also reported that discontinuing Paracetamol reduced pain intensity, and sleep quality improved. The approach included requesting the patient to keep a "pain diary" for better monitoring of symptom progression, and all other measures were maintained.

05/04/2022: Headache continued to improve after the patient stopped taking Paracetamol, reporting only two episodes where Naproxen was needed. The patient did not use Amplictil 4%. The approach included instructing the patient to28/06/2022: After more than two months following the treatment, the patient showed symptom stability. She reported improvement in pain when using Amplictil 4% as a rescue medication as needed, without the need for daily continuous use. There was a slight worsening of symptoms in the last 5 days due to stress related to college exams. The approach was maintained.

18/10/2022: The patient came for a follow-up on the migraine headache. She had not been taking medications (Topiramate, Amitriptyline, Amplictil, and Propranolol) for 20 days because she was without a medical prescription. During this period, she claimed not to have experienced changes in the pain pattern, stating that the medications did not actually help her in this regard. She reported daily pain, nausea, vomiting, photophobia, and phonophobia. She used Dipyrone every 12 hours since August, with mild improvement in pain that returned after 6 hours. ISDA: insomnia. Physical examination revealed a good general condition, conscious and oriented in time and space, afebrile, non-jaundiced, and non-cyanotic. The approach included Dipyrone 500mg every 12 hours if she feels pain, Propranolol 40mg, half a tablet in the morning, and Topiramate 25mg at night.

Hematology: 13/05/2022: The patient, currently 24 years old, was referred by the nephrologist for evaluation of chronic anemia not related to chronic kidney disease (CKD). The patient reported that two months ago, she had started treatment for iron-deficiency anemia using Noripurum but had to discontinue the Neutrofer medication due to nausea and diarrhea, with no improvement in laboratory results for anemia. She complained of fatigue and dyspnea with moderate exertion, which were associated with difficulty breathing through the nose and the use of a mask. The patient denied gingival, urinary, or fecal bleeding. She reported intense and prolonged menstruation for eight days, leading her to consult a gynecologist, who prescribed contraceptive medication to reduce the flow. However, due to the use of Amato, she had to stop the treatment, and the flow returned to its previous intensity. Physical examination: BMI 22.6; blood pressure: 110/70 mmHg. Cardiac auscultation: normal heart sounds, rhythmic in 2 phases, with a holosystolic murmur in the aortic focus. Pulmonary auscultation: bilateral present vesicular murmur, without adventitious sounds. Hemogram (02/2021):Hb: 10.7Ht: 32.7RBC: 4.42VCM: 74HCM: 24.2CHCM: 32.7RDW: 14%Leukocytes: 15,010Platelets: 38,800Segmented Neutrophils: 90%

(08/2021): Hb: 9.4Ht: 29.9VCM: 70.6HCM: 22.1CHCM: 31.4RDW: 14.2%Leukocytes: 8,000Platelets: 300,067Segmented Neutrophils: 64%
(02/2022): Hb: 9.9Ht: 30.9VCM: 73.4HCM: 23.5CHCM: 32RDW: 15.1%Leukocytes: 8,900Platelets: 300,000Segmented Neutrophils: 70%Serum Iron: 76Ferritin: 144
(03/2022): Hb: 9.6Ht: 29.8VCM: 73.1HCM: 23.5CHCM: 32.2RDW: 15.1%Leukocytes: 8,700Platelets: 402,000Segmented Neutrophils: 57%Serum Iron: 54Ferritin: 143

Management: Request for new laboratory tests including complete blood count, reticulocytes, serum iron, ferritin, transferrin, TIBC, transferrin saturation, as well as protein electrophoresis and G6PD analysis (glucose-6-phosphate dehydrogenase). Urgent referral to Gynecology for evaluation of menorrhagia. Referral to nutrition.Follow-up with the hematologist after the gynecology assessment and completion of the prescribed tests.

10/06/2022: Patient returned with results of laboratory tests, reporting sporadic bleeding from the tongue without a specific cause, appearance of mouth lesions, and bleeding after brushing teeth or eating. Additionally, reported a decrease in menstrual flow due to the use of contraceptives prescribed by the gynecologist for one month. Persistent bilateral lower back pain was mentioned, untreated with any medication. Recurrent urinary tract infections (UTIs) with dysuria and polyuria were also reported, with antibiotics used for five days leading to complete improvement. Tests on 13/05/2022 revealed:Hb: 10.8VCM: 70.2HCM: 23.4RDW: 15.2%Leukocytes: 8,710Platelets: 416,000Segmented Neutrophils: 5,077Reticulocytes: 0.6Serum Iron: 20Ferritin: 14Transferrin: 313.

Management: Prescribed Noripurum intravenously, two vials with 250ml of saline each per week for three months.Requested a new hemogram with a count ofHemogram with reticulocyte Count, Serum iron levels, Ferritin levels, Transferrin levels, C-reactive protein (PCR). The patient was referred to nutrition with the need for a follow-up in four months.

DISCUSSION

A syndrome, described in 1969 by Robinow, Silverman, and Smith, is an extremely rare genetic condition with an incidence of 1:500,000 live births. It is characterized by limb shortening and anomalies of the skull, face, and external genitalia. Affecting an equal proportion of men and women and showing low prevalence due to the premature death of 5 to 10% of patients. There are two forms of the disorder: dominant and recessive. In the dominant disorder, patients usually exhibit moderate symptoms, while recessive cases have more characteristic and severe clinical manifestations. The differential diagnosis between these two forms is based on the presence of rib fusions, a condition exclusively found in the recessive variant. Biallelic variants in the Tyrosine Kinase Like Orphan Receptor 2 (ROR2) and Nucleoredoxin (NXN) receptor genes have been implicated as causative genes for the recessive forms of this syndrome. Patients with NXN variants have milder bone defects compared to those related to the ROR2 gene. The genes responsible for the dominant form are WNT5A variants. The patient in this case presents the milder form of the syndrome, the dominant or type 2, as there is no rib fusion. The syndrome has a wide clinical spectrum, including low stature, mesomelic limb shortening, brachydactyly with shortened distal phalanges and hypoplasia or dystrophy of the nails, clinodactyly, which are common symptoms in both dominant and recessive forms. Vertebral segmentation deficiencies are common, more severe in the recessive form (hemivertebrae and scoliosis being the most frequent). Individuals affected by this syndrome have a face resembling that of an 8-week-old fetus: a relatively small face, laterally spaced eyes, and anteriorly facing nostrils. The analyzed patient is 137 centimeters tall and weighs around 40 kilograms, confirming the characteristic low stature of the syndrome. Although she has a bicornuate uterus, the patient has a "typically female vulva," as per the gynecology outpatient consultation, indicating no alterations in external genitalia in this specific case.

Furthermore, there are manifestations through dental and oral alterations, such as dental crowding, irregular teeth, or even supernumerary teeth, an inverted "V" shaped lip showing the upper incisors, usually hyperplastic gums, micrognathia, and ankyloglossia. Regarding facial features, individuals with this condition may have hypertelorism, midfacial hypoplasia, broad nasal bridge, short and upturned nose, and anteverted nostrils. The patient in this study had undergone 8 orofacial surgeries by the age of 8, including gingivoplasty, extraction of malformed teeth, and tongue reconstruction. Moreover, renal alterations may appear, such as hydronephrosis, which may predispose to urinary tract infections, as well as cystic dysplasia of the kidney. Another point to highlight is regarding cardiac changes, such as congenital heart disease, which

may lead to atrial septal defect, coarctation of the aorta, tetralogy of Fallot, atresia or stenosis of the pulmonary valve, and tricuspid valve atresia. Therefore, it is important to screen for congenital heart defects at birth, as they are the main cause of mortality in the first years of life for these patients. The patient studied does, in fact, have recurrent urinary tract infections and, as will be seen from the patient's perspective, fears having a heart condition that she believes could lead to her death, although she is already 25 years old. The heart condition is under investigation. Regarding the neurological system, most individuals have normal cognitive functions, although a delay may exist in up to one-fifth of cases. Macrocephaly is commonly found in Robinow Syndrome and does not indicate a risk factor for developmental delay. The patient analyzed in this case study does, in fact, have macrocephaly, without delays in cognitive development. There are no specific tests or biological markers that specifically characterize the disease. Therefore, the diagnosis is based on clinical presentation, mainly on finding the "fetal face," but radiological examination is necessary to confirm the presence of skeletal malformations. In addition, such clinical findings are of utmost importance to determine the autosomal inheritance of the disease and also to exclude differential diagnoses with syndromes that present similar clinical manifestations.

Another aspect is the prenatal diagnosis, from the 19th week of gestation, made through fetal ultrasonography, which will show skeletal alterations, but the severity of the syndrome is difficult to determine during such an examination. It is important to provide genetic counseling to analyze the possible presence of genetic mutations that explain the origin of the syndrome. The reduced incidence of Robinow Syndrome is greatly influenced by underdiagnosed cases. This occurs mainly due to the lack of knowledge of this syndrome by healthcare professionals, the small number of reported cases, and its low incidence worldwide. Additionally, there is a great clinical variability among affected individuals, making the diagnosis challenging. Currently, there is no cure for the syndrome, so the therapeutic management focuses on resolving medical complications. A patient consistently seeks treatment for complications related to Robinow Syndrome. She has always understood her condition as that of a person with physical disabilities, acknowledging her physical, mental, and cognitive limitations. However, this has not adversely affected her mental health in terms of accepting this condition. She perceives that her family has an extra level of care and concern for her, although she has never questioned them about how they feel having a family member with a disability. Over 25 years, she has observed periods of improvement and some of worsening symptoms. Headaches have been the most inconvenient, as they incapacitate her from carrying out her daily activities on most days, causing functional impairment. Due to the limited improvement with the use of various medications for this issue, she continues in therapeutic trials to find the medication that will provide better relief from headaches, without believing in short-term improvement. As she is undergoing investigation for cardiopathy, she believes that this complication may lead to her demise. However, she remains hopeful in continuing with the investigation and treatment of other conditions.

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