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Case Report
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# Cartilage Hair Hypoplasia and Atypical SCID: A Case Report

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## Abstract

Cartilage Hair Hypoplasia (CHH) is an autosomal recessive genetic disorder, characterized by skeletal abnormalities, thin and sparse hair, immune dysfunction, cognitive deficiency and in some cases, associated with Hirschsprung's disease. CHH is caused by biallelic pathogenic variants in the RMRP gene on chromosome 9p13.3 which impairs lymphocyte cell growth and accelerated apoptosis, resulting in immunodeficiency.

This case is atypical. Our patient had low lymphocyte levels on flow cytometry, abnormal NBS/T Cell Receptor Excision Circles (TREC) count, abnormally low Recent Thymic Emigrants (RTEs) and low naive T-cells on lymphocyte subset panel and known RMRP mutation indicates probable atypical, or leaky, SCID predisposing her to opportunistic infection. Upon further investigation for immune phenotyping, IgG and IgM were normal with absent IgA. There was no evidence of a monoclonal T cell population on T Cell clonality screening by PCR.

**Keywords: Cartilage Hair Hypoplasia; Atypical SCID; Cartilage-hair hypoplasia – an auxetic dysplasia; RMRP mutation; T Cell Receptor Excision Circles; Rhizomelic limbs; Opportunistic infection; IgA**

## Introduction

Cartilage Hair Hypoplasia (CHH) is an autosomal recessive genetic disorder, characterized by skeletal abnormalities, thin and sparse hair, and immune dysfunction, cognitive deficiency and in some cases, associated with Hirschsprung's disease [1]. The orthopedic symptoms are a result of metaphyseal chondrodysplasia, which causes the limbs to be disproportionately short limb dwarfism, hypermobility of joints and/or ligament laxity, and lumbar lordosis [2]. Radiographic findings in patients with CHH-AD spectrum disorder include variable cone-shaped epiphyses metaphyseal dysplasia, premature epiphyseal fusions of the hand, short tubular bones, bowed femora and tibia, and "bullet"- shaped middle phalanges [3].

CHH is caused by biallelic pathogenic variants in the RMRP gene (non-coding mRNA involved in call cycle) on chromosome 9p13.3 [2,4]. A mutation in the RMRP gene leads to an interruption in the cell cycle. When this mutation affects lymphocytes, it results in impaired cell growth and an increase in cell death, which in turn weakens the immune system. Immunodeficiency impacts cell-mediated immunity in various ways, from neutropenia and lymphopenia to severe combined immune deficiency. It also leads to abnormal erythrocytogenesis and increases the likelihood of developing lymphoma [4]. We are reporting a case of CHH with atypical Severe Combined Immunodeficiency (SCID) in a Hispanic patient.

## Case Presentation

A term female born at 37 weeks of gestation to a 38-year-old (Gestations 2, Term 2, Preterm 0, Abortion 0, Living 2) Hispanic mother. Pregnancy was complicated by chronic hypertension and fetal growth restriction. There were no reported teratogenic exposures including alcohol, tobacco, and drugs of abuse. Ultrasounds including estimated amniotic fluid volume were reportedly abnormal for skeletal dysplasia, fetal growth restriction due to short, long bones (micromelia), and breech presentation. Noninvasive prenatal genetic screens were reportedly not obtained. There were additional invasive prenatal genetic tests obtained *via* amniocentesis including normal chromosome analysis and chromosome microarray, and whole genome sequencing that identified compound heterozygous pathogenic (and likely pathogenic) variants in the gene RMRP confirming the diagnosis of Cartilage-Hair Hypoplasia – an Auxetic Dysplasia (CHH-AD) spectrum disorders (Figure 1). The family history was overall non-contributory. Parents are not known to be consanguineous.

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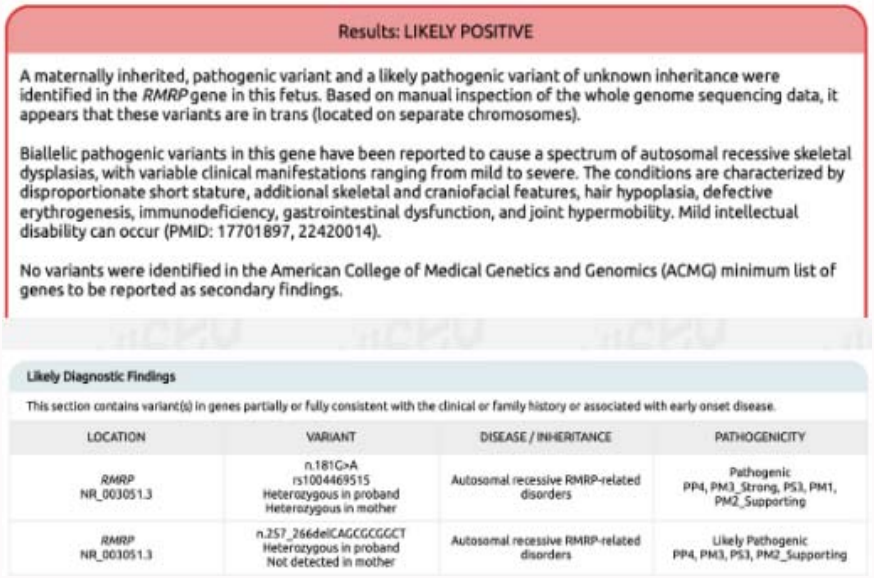


**Figure 1:** Whole genome sequencing completed prenatally identified compound heterozygous pathogenic (and likely pathogenic) variants in the gene RMRP giving the diagnosis of CHH.

**Table 1:** Complete blood count at 10 days of life and 2 months of age.

| CBC | 10 days of life | 2 months of age | Reference Range |
|---|---|---|---|
| Hemoglobin | 11.9 | 11.9 | 9.5-13.5 g/dL |
| Hematocrit | 33.4 | 35.5 | 29.0-41.0% |
| Platelets | 455 | 626 | 135-361 × $10^3$/uL |
| White Cell Count | 13.07 | 5.31 | 6.0-17.5 × $10^3$/uL |
| Neutrophils | 78 | 48 | 20-48% |
| Lymphocytes | 7 | 37 | 34-88% |
| Eosinophils | 0 | 1 | 0-3% |
| Monocytes | 9 | 14 | 0-5% |

**Table 2:** Lymphocyte Subset Assay at 10 days of life and 2 months of age.

| Lymphocyte Subset Assay | 1 week of life cells/uL | 2 months of age cells/uL | Reference Range cells/uL |
|---|---|---|---|
| Absolute CD3 | 303 | 624 | 2500-5500 |
| Absolute CD4 | 195 | 318 | 1600-4000 |
| Absolute CD8 | 94 | 238 | 560-17000 |
| CD4:CD8 Ratio | 2.1 | 1.3 | 1.3-6.3 |
| Absolute CD19 | 281 | 344 | 300-2000 |
| Absolute CD16+56 | 258 | 969 | 170-1100 |

The baby was delivered by C-Section due to breach presentation. Birth weight was 2.520 kg, birth length was 38 cm and head circumference were 34 cm. On the physical exam, baby has proximal rhizomelic shortening of her limbs and bilateral contractures of her wrists (Figure 2). Her hair was thin, curly and fragile in appearance. She was admitted to NICU for hypoglycemia and respiratory distress due to Transient Tachypnea of Newborn (TTN).

Pediatric surgery was consulted on the 1st day of life for presentation of neonatal bowel obstruction. Due to the Association of Hirschsprung's disease with CHH, GI decompression, rectal irrigation, barium enema and full-thickness rectal biopsy were performed, confirming the diagnosis and patient underwent laparoscopic diverting loop colostomy.

**Table 3:** Immunoglobulin Panel at 10 days of life and 2 months of age.

| Immunoglobulin Panel | 1 week of life (mg/dL) | 2 months of age (mg/dL) | Reference Range |
|---|---|---|---|
| IgA | <7 | <7 | 3-47 mg/dL |
| IgG | 713 | 514 | 206-601 mg/dL |
| IgM | 25 | 34 | 17-89 mg/dL |

Babygram was consistent with shortened long bones and streaky infiltrates. Genetics was consulted due to skeletal dysplasia. They recommended skeletal survey as well as consulting Pediatric Immunology since CHH-AD includes risks for immunodeficiency. The skeletal survey findings were consistent with CHH.

Her immunodeficiency workup recommended by Pediatric Immunology showed normal CBC (Table 1), low CD3, CD4, CD8, and CD19+ lymphocytes (Table 2). The lymphocyte proliferation assay to mitogen could not be obtained due to critically low lymphocyte levels in the peripheral blood. These low lymphocyte levels on flow cytometry, in conjunction with the abnormal NBS/T Cell Receptor Excision Circles (TREC) count, abnormally low Recent Thymic Emigrants (RTEs) and low naive T-cells on lymphocyte subset panel and known RMRP mutation indicates probable atypical, or leaky, SCID predisposing her to opportunistic infection. Upon further investigation for immune phenotyping, IgG and IgM were normal with absent IgA (Table 3). There was no evidence of a monoclonal T cell population on T Cell clonality screening by PCR.

Pediatric Infectious Disease recommended reverse isolation (gown/glove/mask and scrub for people entering room for patient care activities), RSV prophylaxis, herpesvirus prophylaxis with acyclovir 12.5 mg/kg BID, and fluconazole prophylaxis 6 mg/kg/day. Pneumocystis prophylaxis with trimethoprim-sulfamethoxazole started at 4 weeks of age at 2.5 mg/kg of the trimethoprim component BID two times per week as well as folinic acid 1.25 mg daily twice per week to help minimize neutropenia related to this prophylaxis. Urine and blood CMV were negative. These recommendations are consistent with a national consortium of primary immunodeficiency treatment centers [5].

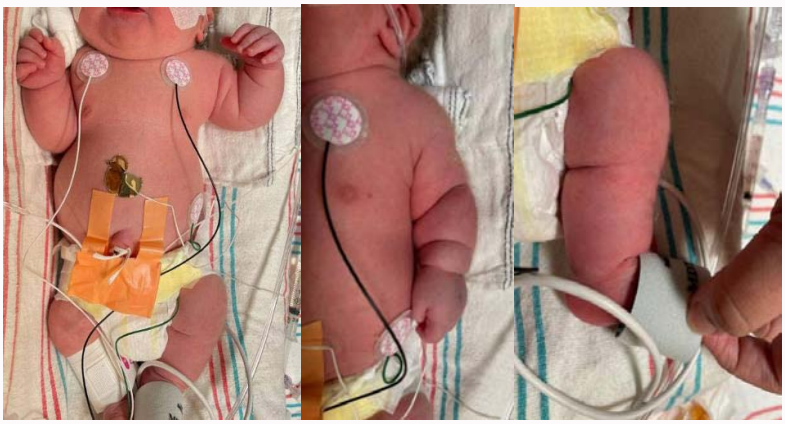

**Figure 2:** Proximal rhizomelic shortening of her limbs and bilateral contractures of her wrists.

Patient received 1 dose of IVIG 0.5 mg/kg prior to discharge, in addition to continuing antimicrobial prophylaxis for SCID. Upon discharge, patient was referred to immunology/bone marrow transplant team regarding continued care. Upon Follow up, baby was adequately gaining weight, mom was compliant with medication as well as keeping up with appointments. Patient was up to date with vaccine besides live vaccines since they were contraindicated with SCID. Her ostomy was checked by surgery on which looked intact and had no evidence of infection.

Patient was scheduled for monthly Immunology follow up to initiate Immunoglobulin (IG) replacement therapy, which was discussed with family while awaiting bone marrow transplant. Family preferred she receive subcutaneous IG therapy. Immunology team initiated Hizentra 1g/5 mL 8.5 mL subcutaneous every 2 weeks. Her prophylactic Fluconazole, Acyclovir, Sulfamethoxazole-Trimethoprim and Folic Acid was continued. Repeated lymphocyte subset assay at 2 months of age showed relative improvement in cell count (Table 2). Immunoglobulins levels were unchanged (Table 2). CBC showed leucopenia (Table 1). An informed written consent was obtained from parents before writing this case report. Figure 1, 2 taken from patient's chart with parental consent.

## Discussion

Immunodeficiency is one of the known complications of CHH due to defective proliferation or function of T-cells predisposing them at risk of opportunistic infections. It generally spares humoral immunity, but the study done in Finland mentioned that these patients may have low IgG and undetectable IgA [3]. This was also seen in our patient as she had undetectable IgA levels with normal IgG and IgM levels. CHH with SCID predisposes a patient to chronic bronchiectasis which is even seen in patients with mild immunodeficiency [3]. Therefore, patients with CHH should be screened by progression of immunodeficiency from time to time. Management is mainly focused on primary prevention with vaccination while avoiding live attenuated vaccines. Antimicrobial prophylaxis and immunoglobulin therapy is also recommended. All together, these recommendations are emphasized overtime by multiple studies [5,6]. These patients will benefit the best from Hematopoietic Stem Cell Transplantation (HSCT). Our patient will be following another tertiary care hospital for HSCT [7]. Although HSCT is indicated in patients with CHH and SCID, these patients should receive transplant before developing opportunistic infections, end organ damage or malignancy.

Patients with CHH with SCID have abnormal newborn screen due to absent or low TREC counts. 1st newborn screen for our patient flagged for abnormally low TREC and 2nd newborn screen for undetectable TREC. Recent studies suggested closer correlation with TREC or newborn screen with level of immunodeficiency [6] but there are not enough studies to support TREC as a prognostic indicator in SCID [7].

CHH presentation varies over a spectrum of orthopedic, infectious, endocrinologic, pulmonary, hematologic, gastrointestinal, as well as rehabilitation issues therefore there should be multidisciplinary approach towards the management of these patients.

## Conclusion

Even though CHH is recognized for its link to immunodeficiency, the prompt and appropriate treatment of SCID with antimicrobial prophylaxis and IVIG significantly alters the course of the disease. It enhances patient outcomes in terms of morbidity and mortality as they await a bone marrow transplant.

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