International Journal of Nutrology
(Official Journal of the ABRAN - Brazilian Association of Nutrology)

CASE REPORT

DOI: 10.54448/ijn24403

MDPL syndrome (mandibular hypoplasia, deafness, progeroid features, and lipodystrophy) and nutrological management: a rare case report

Limiro Luiz da Silveira Neto[1*]

[1] SHN, Quadra 1, Bloco B. Saint Moritz Hotel, Apto 1913. Asa Norte, Brasília, Distrito Federal, Brazil.

*Corresponding author: Dr. Limiro Luiz da Silveira Neto.
SHN, Quadra 1, Bloco B. Saint Moritz Hotel, Apto 1913.
Asa Norte, Brasília, Distrito Federal, Brazil, CEP 70701000.
E-mail: drlimiro@hotmail.com

DOI: https://doi.org/10.54448/ijn24403

Received: 07-13-2024; Revised: 09-07-2024; Accepted: 09-11-2024; Published: 09-17-2024; IJN-id: e24403

Editor: Dr. Carla Maria Barreto da Silva de Sousa Rego, MD, MsD, Ph.D.

Abstract

Introduction: Congenital lipodystrophies comprise a rare group of heterogeneous disorders that affect adipose tissue distributions and are characterized by varying degrees of body fat loss. Genetic damage, telomere shortening, cellular senescence, and proliferation defects are hallmarks of the aging process. Metabolism and mitochondrial activity play an important role in the pathogenesis of MDPL syndrome (mandibular hypoplasia, deafness, progeroid features, and lipodystrophy). **Objective:** It was to report the case and diagnosis of a patient with MDPL syndrome and the nutrological management. **Case report:** The information was obtained during the patient's medical consultation with the author, interview with the patient and family, photographic record, and literature review. This study followed ethics committee compliance and preserved the patient's anonymity, as well as the patient's rights and care, as per the 1964 Declaration of Helsinki. The total fat percentage of 32% (54th percentile), a very low relative musculoskeletal index of 2.56 kg/m^2, and also a low fat mass index of 3.89 g/m^2. Laboratory tests showed a low leptin of 1.90 ng/mL, basal insulin of 166.3 µUI/mL, HOMA IR of 38.2, and triglycerides of 205 mg/dL. Analysis of DNA extracted by oral SWAB was positive for alteration in the POLD1 gene, confirming the diagnosis of MDPL. After initiating treatment with a diet adjusted in proteins, calories, index, and glycemic load, metformin, the patient presented new exams with HOMA-IR 8.3, evolving with a gain of 2.5 kilos, now with 33.1 kilograms of weight, reporting improvement. **Final considerations:** The reported case and raised publications bring to light the discussion of the diagnosis and treatment of a complex syndrome such as MDPL. The absence of a cure, the difficulty in diagnosis, and the unavailability of some of the therapeutic resources make the syndrome of mandibular hypoplasia, deafness, progeroid characteristics, and lipodystrophy an extremely rare syndrome, difficult to diagnose, and difficult to manage. Progress in identifying lipodystrophy genes will help to better understand the role of pathways involved in the complex physiology of fat. Studies have shown mitochondrial dysfunction as well as morphological alterations in mitochondria in patients with MDPL.

Keywords: Lipodystrophy. Low weight. Mandibular hypoplasia. Deafness. Progeroids. POLD1.

Introduction

Congenital lipodystrophies comprise a rare group of heterogeneous disorders that affect adipose tissue distributions and are characterized by varying degrees of body fat loss (complete and/or partial) and various profound metabolic disorders such as severe insulin resistance, glucose intolerance, diabetes, dyslipidemia, and fatty liver disease **[1]**. Lipodystrophy can be acquired (secondary to some types of diseases or due to the use of certain drugs) or hereditary (autosomal recessive or dominant forms). In the literature, about 1000 patients have been reported as affected by genetic forms of lipodystrophies and their estimated prevalence in the general population is less than 1 in a million **[1-3]**.

The MDPL syndrome (mandibular hypoplasia, deafness, progeroid characteristics, and lipodystrophy) is even rarer with few cases diagnosed in the world (approximately 30 cases), being an autosomal disease characterized by the presence of lipodystrophy associated with mandibular hypoplasia, deafness and progeroid characteristics, caused by changes in the Polymerase Delta 1 (POLD1) gene on chromosome 19 **[4,5]**.

Given this, the objective of this study was to report a case of MDPL in an adult patient aged 37 years without a correct diagnosis and to present the complications presented by the patient.

Methods

Study Design

The present case report study followed the CARE rules – Case Report. Available at: https://www.care-statement.org/. Accessed on: 05/30/2023.

Ethical Approval

This study followed the ethics committee's compliance and preserved the patient's anonymity, as well as preserving the rights and care of the patient and her information as recommended by the Declaration of Helsinki of 1964 and the seventh revision occurred in Fortaleza - Brazil (2013). The information contained in this work was obtained by reviewing the medical records, interviewing the patient, photographing the diagnostic methods to which the patient was submitted, and reviewing the literature, and data were obtained through the collection and analysis of information contained in the patient's medical record, duly authorized by the patient by signing the Free and Informed Consent Form.

Case Report

Patient Information and Clinical Findings, Timeline, Diagnostic Assessment, Therapeutic Intervention and Follow-up

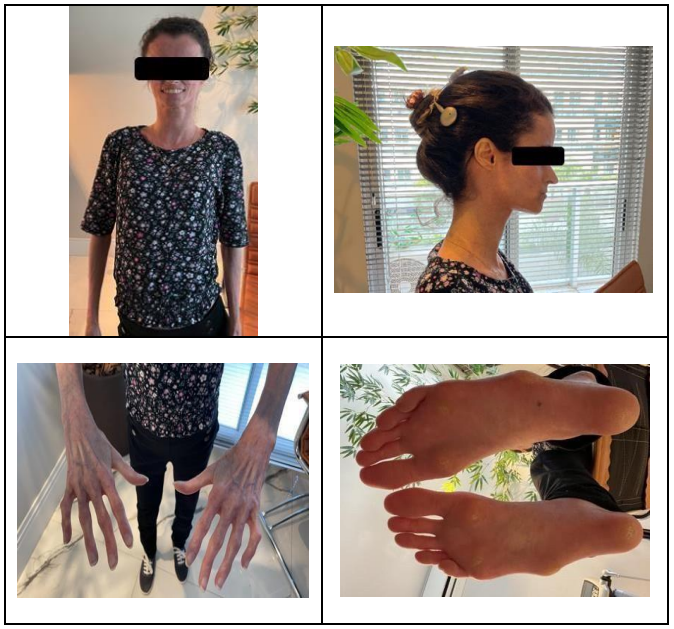
Anamnesis

Patient S.N.G, 37 years old, comes to the office with the desire to gain weight. She complains of fatigue and difficulty gaining lean mass and fat even with a previous diet prescribed by professionals. She reports the onset of hearing changes and low weight since childhood, which worsens after 10 years of age when skin changes also appear. Menarche at age 13 with regular cycles, but with heavy flow, and preserved appetite, She performs physical exercises at home sporadically following videos on the internet, and denies smoking or alcoholism. In the previous pathological history, she reports previous deafness with a cochlear implant and diagnosis of scleroderma, she only used cholecalciferol 2000 UI/day and sporadic omega-3.

Physical Exam

Physical examination showed a somatotype of ectomorphy, presence of cochlear implant, progeroid characteristics, high-pitched voice, generalized consumption of adipose tissue and low muscle mass even though function was preserved in the tests performed, absence of breasts bilaterally, hardened skin, weight of 30.6 kilos, height of 156 centimeters and Quetelet index of 13 kg/m^2, also showing alterations in the curvature and shape of the hands and feet (Figure 1).

Figure 1. Clinical examination showing the somatotype of ectomorphy and alterations in the curvature and shape of the hands and feet.



Source: Own authorship.

Diagnostic hypothesis

Taking into account the expressive reduction of adipose tissue, auditory alterations, and together with the anamnesis and the findings in the physical examination, the hypothesis of MDPL syndrome was raised and the laboratory tests were requested to confirm the diagnosis, including the genetic test.

Exams

Whole-body dual-energy X-ray absorption demonstrated a total fat percentage of 32% (54th percentile), a very low relative musculoskeletal index of 2.56 kg/m^2, and a low-fat mass index of 3.89 gsm. Laboratory tests showed a low leptin of 1.90 ng/mL, basal insulin of 166.3 µUI/mL, HOMA IR of 38.2, and

triglycerides of 205mg/dL. Analysis of DNA extracted by oral SWAB was positive for alteration in the POLD1 gene, confirming the diagnosis of MDPL.

After initiating treatment with a diet adjusted in protein, calories, index, and glycemic load, metformin, the patient underwent new tests with HOMA-IR 8.3, evolving with a gain of 2.5 kilos, now weighing 33.1 kilograms and still without other exams, reporting improvement.

Discussion

The failure found by the patient in gaining weight, even following all the guidelines in several previous consultations, is justified by the diagnosis hitherto unknown to her. One of the treatments for lipodystrophy is the use of leptin, but it is still inaccessible due to the very high cost, making the treatment of the syndrome even more difficult.

In this scenario, aging is an extremely complex biological process. The accumulation of DNA damage and its consequences progressively interfere with cellular function and increase susceptibility to the development of aging. Delta DNA polymerase (Pol δ), encoded by the POLD1 gene at 19q13.3, is well implicated in many steps of the replication and repair program. Thanks to its exonuclease and polymerase activities, the enzyme is involved in cell cycle regulation, DNA synthesis, and DNA damage repair processes. Harmful variants within the exonuclease domain predispose to cancer, while those occurring at the polymerase active site cause the autosomal dominant progeroid syndrome called MDPL, mandibular hypoplasia, deafness, and progeroid features with concomitant lipodystrophy. An overview of the critical activities of Pol δ will allow us to better understand the associations between DNA damage and almost all aspects of the aging process **[6]**.

In this sense, lipodystrophies are a large heterogeneous group of genetic or acquired diseases characterized by generalized or partial loss of fat, usually associated with metabolic complications such as diabetes mellitus, hypertriglyceridemia, and hepatic steatosis. One study reported the clinical description of a woman with a rare severe lipodystrophy and progeroid syndrome associated with hypertriglyceridemia and diabetes whose genetic underpinnings were clarified through whole exome sequencing (WES) analysis. This article presents the 5th MDPL patient (mandibular hypoplasia, deafness, progeroid features, and lipodystrophy syndrome) with the same p.S605del mutation in POLD1. This genetic evidence reveals that this is a disease-causing mutation **[7]**.

Another case report showed that diabetic retinopathy was detected as the primary manifestation in a Chinese girl with MDPL syndrome who carried a known POLD1 mutation (c.1812_1814delCTC, p.Ser605del). The typical features of the syndrome were detected after comprehensive examinations. The patient suffered from blurred vision and eye pain due to neovascularization of the retina (vitreous hemorrhage and retinal detachment) and the iris (neovascular glaucoma). The literature review revealed that the prevalence of hepatomegaly and abnormal triglyceride levels was significantly higher in women than in men with MDPL syndrome carrying POLD1 mutations **[8]**.

In this context, genetic damage, telomere shortening, cellular senescence, and proliferation defects are important in the aging process. Since a clear connection between telomere shortening and mitochondrial malfunction to initiate the aging process has been reported, it is evidence that mitochondrial metabolism and activity play an important role in the pathogenesis of MDPL Syndrome. The mtDNA copy number was evaluated, evaluating a significant decrease in the mutated cells. The level of expression of genes related to biogenesis and mitochondrial activity also revealed a significant reduction, highlighting mitochondrial dysfunction in MDPL cells. Also, the levels of expression of the mitochondrial marker SOD2, by immunofluorescence, were reduced. The decrease of this antioxidant enzyme correlated with increased mitochondrial ROS production in MDPL cells. Also, Scanning Electron Microscopy/Focused Ion Beam analysis revealed fewer mitochondria in MDPL cells and with morphological abnormalities. Autophagic vacuoles containing partially digested mitochondria were detected. Metformin administration, although unable to restore mitochondrial impairment, proved to be efficient in rescuing nuclear abnormalities, suggesting its use to specifically improve the premature aging phenotype **[9]**.

Also, a japanese woman was diagnosed with MDPL using whole exome sequencing analysis. A mutation in exon 15 (p.Ser605del) of the POLD1 gene was identified. The results provide additional evidence that POLD1 mutations are responsible for the MDPL syndrome and serve as a common genetic determinant across different ethnicities **[10]**.

Final Considerations

The reported case and raised publications bring to light the discussion of the diagnosis and treatment of a complex syndrome such as MDPL. The absence of a cure, the difficulty in diagnosis, and the unavailability of some of the therapeutic resources make the syndrome of mandibular hypoplasia, deafness, progeroid

characteristics, and lipodystrophy an extremely rare syndrome, difficult to diagnose, and difficult to manage. Progress in identifying lipodystrophy genes will help to better understand the role of pathways involved in the complex physiology of fat. This will lead to new goals for the development of innovative therapeutic strategies for the treatment of the disease and its metabolic complications, as well as more common forms of adipose tissue redistribution, as seen in metabolic syndrome and type 2 diabetes. Diabetic retinopathy is a complication of MDPL syndrome. Hepatomegaly and abnormal triglyceride levels are more common in female patients with MDPL syndrome. Finally, studies have shown mitochondrial dysfunction, as well as morphological alterations in mitochondria in patients with MDPL.

CRediT

Author contributions: **Conceptualization -** Limiro Luiz da Silveira Neto; **Data curation -** Limiro Luiz da Silveira Neto; **Formal Analysis -** Limiro Luiz da Silveira Neto; **Investigation -** Limiro Luiz da Silveira Neto; **Methodology -** Limiro Luiz da Silveira Neto; **Project administration -** Limiro Luiz da Silveira Neto; **Supervision -** Limiro Luiz da Silveira Neto; **Writing - original draft -** Limiro Luiz da Silveira Neto; **Writing- review & editing-** Limiro Luiz da Silveira Neto.

Acknowledgment

Not applicable.

Ethical Approval

This study followed the ethics committee's compliance and preserved the patient's anonymity, as well as preserving the rights and care of the patient and her information as recommended by the Declaration of Helsinki of 1964 and the seventh revision occurred in Fortaleza - Brazil (2013).

Informed Consent

This study followed the ethics committee's compliance and preserved the patient's anonymity, as well as preserving the rights and care of the patient and her information as recommended by the Declaration of Helsinki of 1964 and the seventh revision occurred in Fortaleza - Brazil (2013).

Funding

Not applicable.

Data Sharing Statement

No additional data are available.

Conflict of Interest

The authors declare no conflict of interest.

Similarity Check

It was applied by Ithenticate®.

Peer Review Process

It was performed.

References

1. Pelosini C, Martinelli S, Ceccarini G, Magno S, Barone I, Basolo A, Fierabracci P, Vitti P, Maffei M, Santini F. Identification of a novel mutation in the polymerase delta 1 (POLD1) gene in a lipodystrophic patient affected by mandibular hypoplasia, deafness, progeroid features (MDPL) syndrome. Metabolism. 2014 Nov;63(11):1385-9. doi: 10.1016/j.metabol.2014.07.010.
2. Fiorillo C, D'Apice MR, Trucco F, Murdocca M, Spitalieri P, Assereto S, Baratto S, Morcaldi G, Minetti C, Sangiuolo F, Novelli G. Characterization of MDPL Fibroblasts Carrying the Recurrent p.Ser605del Mutation in POLD1 Gene. DNA Cell Biol. 2018 Nov 2. doi: 10.1089/dna.2018.4335.
3. Elouej S, Beleza-Meireles A, Caswell R, Colclough K, Ellard S, Desvignes JP, Béroud C, Lévy N, Mohammed S, De Sandre-Giovannoli A. Exome sequencing reveals a de novo POLD1 mutation causing phenotypic variability in mandibular hypoplasia, deafness, progeroid features, and lipodystrophy syndrome (MDPL). Metabolism. 2017 Jun;71:213-225. doi: 10.1016/j.metabol.2017.03.011.
4. Coppedè F. Mutations Involved in Premature-Ageing Syndromes. Appl Clin Genet. 2021 Jun 2;14:279-295. doi: 10.2147/TACG.S273525.
5. Yu PT, Luk HM, Mok MT, Lo FI. Evolving clinical manifestations of mandibular hypoplasia, deafness, progeroid features, and lipodystrophy syndrome: From infancy to adulthood in a 31-year-old woman. Am J Med Genet A. 2021 Mar;185(3):995-998. doi: 10.1002/ajmg.a.62035.
6. Murdocca M, Spitalieri P, D'Apice MR, Novelli G, Sangiuolo F. From cue to meaning: The involvement of POLD1 gene in DNA replication, repair and aging. Mech Ageing Dev. 2023

Apr;211:111790. doi: 10.1016/j.mad.2023.111790.

7. Reinier F, Zoledziewska M, Hanna D, Smith JD, Valentini M, Zara I, Berutti R, Sanna S, Oppo M, Cusano R, Satta R, Montesu MA, Jones C, Cerimele D, Nickerson DA, Angius A, Cucca F, Cottoni F, Crisponi L. Mandibular hypoplasia, deafness, progeroid features and lipodystrophy (MDPL) syndrome in the context of inherited lipodystrophies. Metabolism. 2015 Nov;64(11):1530-40. doi: 10.1016/j.metabol.2015.07.022.
8. Zhou L, Lv Z, Tian X, Zhang Y, Xu Z. Eye pain and blurred vision as main complaints in a new case with MDPL syndrome. Eur J Ophthalmol. 2022 Sep;32(5):NP82-NP86. doi: 10.1177/11206721211009179.
9. Murdocca M, Spitalieri P, Cappello A, Colasuonno F, Moreno S, Candi E, D'Apice MR, Novelli G, Sangiuolo F. Mitochondrial dysfunction in mandibular hypoplasia, deafness and progeroid features with concomitant lipodystrophy (MDPL) patients. Aging (Albany NY). 2022 Feb 23;14(4):1651-1664. doi: 10.18632/aging.203910.
10. Sasaki H, Yanagi K, Ugi S, Kobayashi K, Ohkubo K, Tajiri Y, Maegawa H, Kashiwagi A, Kaname T. Definitive diagnosis of mandibular hypoplasia, deafness, progeroid features and lipodystrophy (MDPL) syndrome caused by a recurrent de novo mutation in the POLD1 gene. Endocr J. 2018 Feb 26;65(2):227-238. doi: 10.1507/endocrj.EJ17-0287.