

Hip Dysplasia in a Patient in Late Adolescence With Charcot-Marie-Tooth and Multiple Acyl-CoA Dehydrogenase Deficiency

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Abstract

This case report explores a unique presentation of hip dysplasia in a female patient aged 21 years old diagnosed with Charcot-Marie-Tooth disease (CMT) type 1A and multiple acyl-CoA dehydrogenase deficiency (MADD). The coexistence of these neuromuscular and metabolic disorders in a patient with hip dysplasia provides an opportunity to investigate their potential interactions and impact on diagnosis, treatment, and prognosis. The patient underwent labral repair with shelf osteotomy and later a total hip replacement. This case highlights the need for further research to better understand the relationships between CMT, MADD, neuromuscular dysplasia, and hip dysplasia. A deeper understanding of these interactions may lead to improved diagnostic techniques, earlier intervention, and personalized treatment approaches for patients with co-morbid conditions, ultimately improving patient outcomes and reducing complications later in life.

Keywords: Charcot-Marie-Tooth; Multiple acyl-CoA dehydrogenase deficiency; Hip prosthesis implantation; Orthopedics; Hip dysplasia

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Introduction

Hip dysplasia is a relatively common orthopedic condition involving a spectrum of disorders affecting the hip joint in infants and children. Hip dysplasia can lead to high morbidity and decreased functional status [1]. This condition may coexist with various other syndromes, such as teratologic hip dysplasia and neuromuscular hip dysplasia, which can be frequently encountered in clinical practice.

Charcot-Marie-Tooth disease (CMT) and multiple acyl-CoA dehydrogenase deficiency (MADD) are neuromuscular and metabolic disorders, respectively. CMT or hereditary motor and sensory neuropathy is the most common inherited neuromuscular disorder. It is characterized by abnormal development of the peripheral nerves leading to muscle weakness that may impact hip joint stability [2]. It often presents with a pes cavus deformity (high-arched feet) in the adolescent years presenting numbness in the lower extremities, potentially leading to unintentional injury/ulceration, akin to that seen in diabetic peripheral neuropathy.

MADD is a rare autosomal recessive metabolic myopathy, characterized by impaired dehydrogenation reactions due to defective electron transfer from flavoprotein dehydrogenases to the mitochondrial respiratory chain. This results in a variety of consequences, which may present as: muscle weakness and poor exercise tolerance for age, lethargy, hypoglycemia, metabolic acidosis, and hepatomegaly [3].

Predominantly affecting cellular respiration and production of cellular energy resources, impacting tissues with high energy requirements, such as muscles, the coexistence of these conditions in a patient with hip dysplasia presents a unique opportunity to explore their potential interactions and their impact on the patient's diagnosis, treatment, and prognosis. This case report illustrates a unique presentation of hip dysplasia in a female patient aged 21 years old diagnosed with CMT type 1A and MADD.

Case Report

Investigations

A female in her late adolescence presented to the emergency department with a 2-month history of right hip pain. The pain

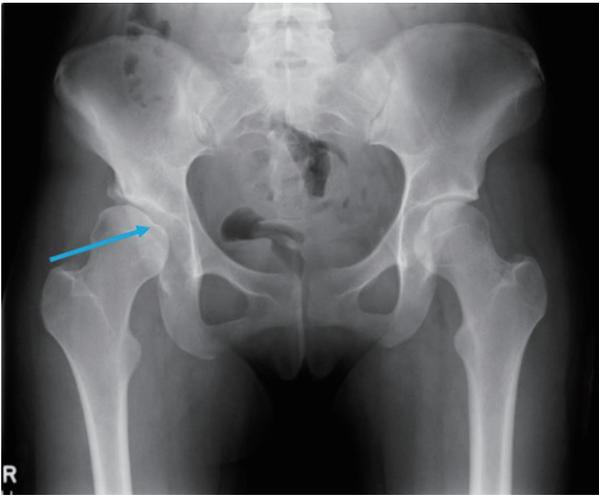


Figure 1. A plain radiograph taken during the first visit to the emergency department (ED), revealing right hip dysplasia, with uncovering of the lateral side of the femoral head and early secondary degenerative changes (blue arrow), and a normal appearance to the left hip on radiograph.

was specifically around the anterior and posterior aspects of the groin region. Her past medical history included CMT type 1A, MADD, asthma, adrenal insufficiency, inherited neuropathy, idiopathic toe walking, pes cavus and hammer toes. The patient had a background of multiple admissions with gastroenteritis and pneumonia. A diagnosis of MADD was suspected due to the family history. Late-onset MADD (type III) is the most common presentation, with signs and symptoms appearing anytime from infancy to adulthood. The patient's genetic analysis for the electron transfer flavoprotein dehydrogenase (ETFHDH) gene, associated with riboflavin-responsive multiple acyl-CoA dehydrogenation deficiency, revealed the presence of a single mutation, which indicated of a carrier status. However, an abnormal plasma acylcarnitine profile, reflecting aberrant myoadenylate deaminase (MAD) enzyme activity, had been observed during a period of illness. It was hypothesized that the 'patient's genetic alteration might have impacted their biochemical profile under specific stressors, such as infections, while remaining normal under other circumstances.

Her family history also indicated the presence of CMT neuropathy in multiple relatives, and the inheritance pattern might instead represent autosomal dominant inheritance with reduced penetrance. Additionally, the patient's paternal family had a history of riboflavin-responsive multiple acyl-CoA dehydrogenation deficiency, a subtype of MADD.

The patient's drug history included riboflavin (vitamin B2), morphine, codeine, zopiclone, omeprazole, cetirizine, prochlorperazine, beclomethasone and salbutamol inhalers, amitriptyline and tramadol.

The patient's childhood and development history included being delivered via cesarean section with a breech presentation. Maternal history also revealed uterus didelphys. An ultrasound scan of both hips performed shortly after birth was reportedly normal. Although, early in her childhood, the patient had problems walking and received orthotic appliance treat-

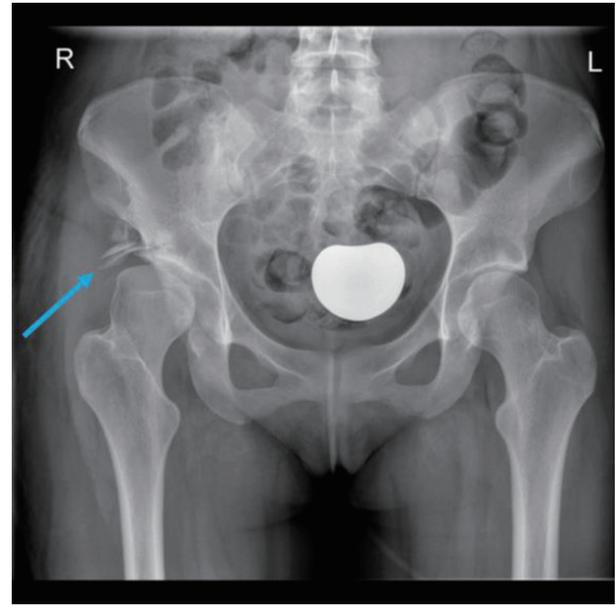


Figure 2. A plain radiograph after right labral repair with shelf osteotomy (blue arrow).

ment, serial ankle casts and botulinum toxin injections. Strong family history of CMT is also noted. She lives with parents and has never smoked and does not drink alcohol.

Diagnosis

On clinical examination, the patient had a thin build with symmetrical musculature in her lower limbs. She had an antalgic gait with normal lower limb alignment and no leg length discrepancy. Her right hip had a good range of movement with pain in extreme abduction and internal rotation.

A plain radiograph taken during her initial visit revealed evidence of right hip dysplasia with Shenton's line intact and uncovering of the lateral side of the femoral head with minimal degenerative changes as illustrated in Figure 1.

The patient initially underwent a shelf osteotomy at the age of 18 years old (Fig. 2), to provide superior and superolateral femoral head coverage, and labral repair. The patient had a good result and was pain-free for 2 years, but the pain progressively returned. Subsequently, a magnetic resonance imaging (MRI) arthrogram of the right hip was performed (Fig. 3), which demonstrated a dysplastic hip with extensive abnormality of the acetabular rim and features of associated acetabular cartilage damage. The images were discussed at a multi-disciplinary meeting, and it was decided that symptomatically and radiologically a total hip replacement was indicated to address her pain and functional limitation, which was performed at the age of 21 years old (Fig. 4).

Follow-up and treatment

The patient has had several flare-ups of MADD and remains

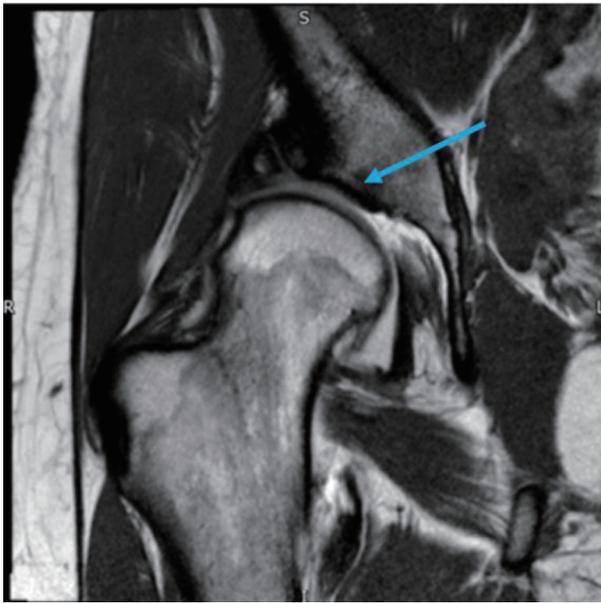


Figure 3. A magnetic resonance imaging (MRI) arthrogram of the right hip revealing a dysplastic hip and features of associated acetabular cartilage damage (blue arrow).

under ongoing monitoring by the endocrinology department at Oxford, with thorough evaluations being conducted at regular intervals. Her case has been referred to multiple multidisciplinary teams (MDTs) for psychological support and pain management, with a particular focus on neurology.

The patient is also currently under biannual surveillance by the chronic pain team at a tertiary center. Plans are being considered for potential discharge to community care, given stable and satisfactory responses to pain management interventions.

The patient has been experiencing challenges with dietary intake and is leaning more towards simple foods. They have been provided with nutritional supplements to help ensure proper nutrition. Additional support is being given by dietitian from a local tertiary team. The patient has been provided comprehensive follow-up care, with a keen focus on their overall health, return to daily activities, and the necessary aftercare arrangements.

Discussion

Hip dysplasia manifests itself in various types distinguished by etiology. Among these classifications are developmental dysplasia of the hip (DDH), neuromuscular developmental hip dysplasia (NMDH) and dysplasia secondary to metabolic or genetic disorders [4].

The terms DDH and NMDH are often used interchangeably. However, their exact relationship remains unclear. Some studies propose shared pathophysiological mechanisms between DDH and NMDH, such as abnormal muscle tone and joint laxity [5, 6]. Conversely, other studies highlight them as distinct conditions [7, 8]. There is general agreement on the increased incidence and severity of hip dysplasia in those with

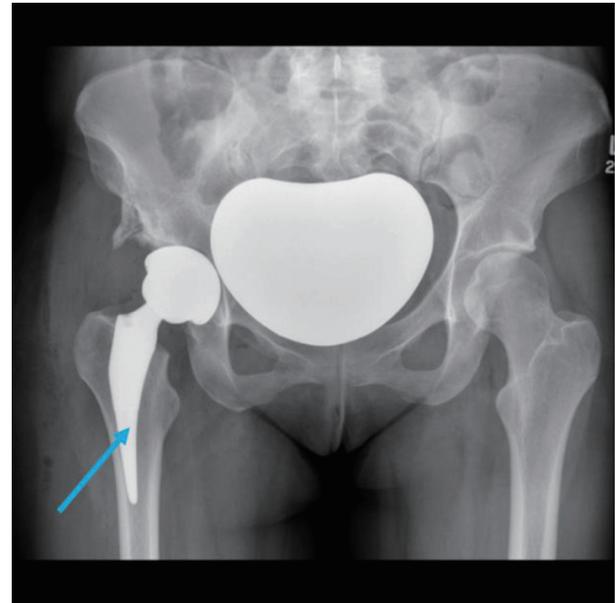


Figure 4. A plain radiograph showing a right total hip replacement (blue arrow).

neuromuscular pathologies. For instance, the incidence of hip disorders is much higher in children with neuromuscular disorders, varying from 8% to 82% [9-11] and that NMDH generally presents later than DDH [10]. Also, the treatment for NMDH is predominantly surgical with some cases requiring numerous operations due to abnormal muscle tone [12, 13].

Different pathophysiologies underpin the disorders associated with upper motor neuron (UMN) and lower motor neuron (LMN) causes of hip dysplasia. In UMN disorders, factors such as spasticity, restricted mobility and functional muscular asymmetry exacerbate abnormalities of the femoral head and acetabulum, resulting in subluxation, dislocation and coxa valga [14-16]. Importantly, the common factors leading to coxa valga in CMT and MADD, are proximal weakness, limited weight-bearing, and ligamentous laxity [17, 18].

Research has highlighted a relationship between CMT and hip dysplasia, with the term Charcot-Marie-Tooth hip dysplasia (CMTHD) often used to describe the coexistence of the two conditions. It has been suggested that CMTHD patients present later in life [19, 20] and greater overall disordered hip morphology compared to that of DDH [21]. Typically, the hips of CMTHD patients are normal at birth unless there is concomitant DDH [22]. Furthermore, CMT patients have been reported with decreased bone mineral density, exacerbating the risk and severity of hip dysplasia [23, 24].

On the other hand, the role of MADD in hip dysplasia remains ambiguous. Characterized by the impairment of flavo-protein enzymes vital for energy production. MADD can lead to muscle weakness and instability of the hip joint due to accumulation of toxic metabolites [25, 26]. Metabolic acidosis, another consequence of MADD, can decrease bone mineral density, heightening susceptibility to deformities and instability (Fig. 5). Therefore, it is possible to suggest that the combination of these two conditions may have led to the NMDH. Other mi-

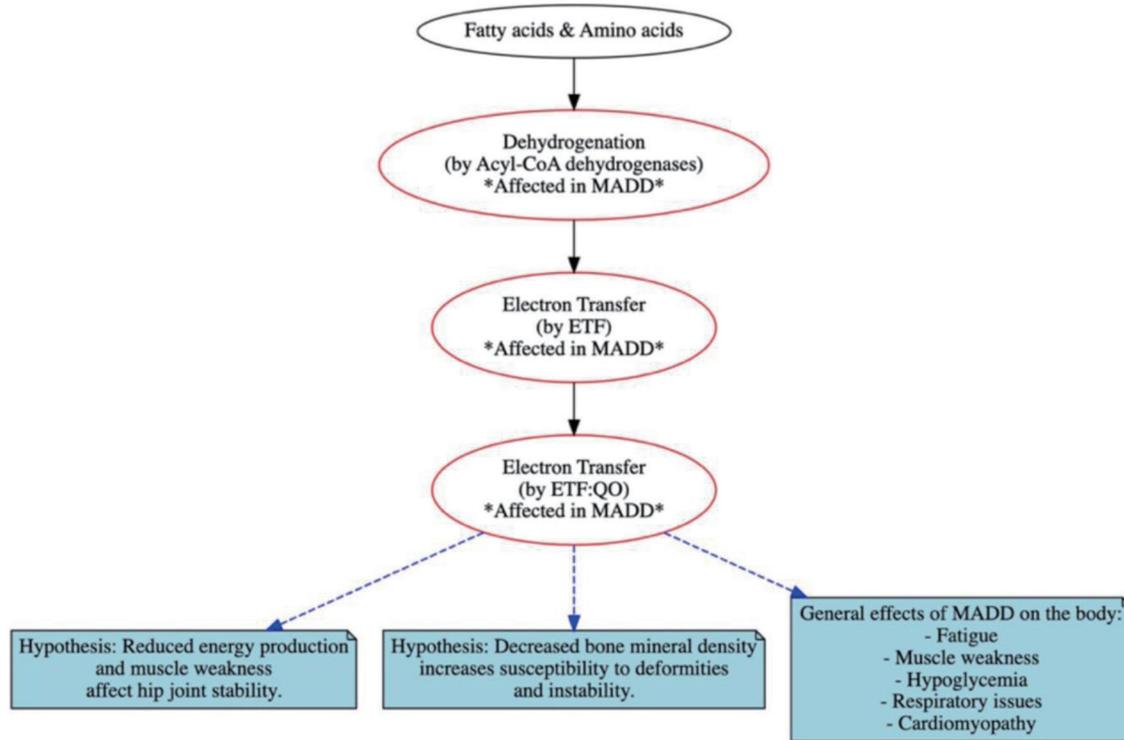


Figure 5. Schematic representation of key abnormalities including flavoprotein dehydrogenase enzymes, electron transfer flavo-protein (ETF) and ETF: ubiquinone oxidoreductase (ETF: QO) with outcomes in multiple acyl-CoA dehydrogenation deficiency (MADD).

nor contributing factors are female sex and breech presentation.

In analyzing this patient’s case, it is pertinent to consider potential confounding factors such as other genetic or environmental influences and the presence of other risk factors such as female sex and breech presentation. The varying severity and manifestation of CMT and MADD add complexity to understanding their impact on hip dysplasia. Born in breech presentation, the complexity is further compounded, highlighting the need for an evolving understanding of the mechanisms underlying CMT, MADD and hip dysplasia.

The unique interplay between NMDH, CMT, and MADD, as reflected in this patient’s case, underscores the intricacy of hip dysplasia. The presentation of ligamentous laxity, limited weight-bearing ability, proximal muscle weakness and decreased bone mineral density depicts the multifaceted nature of her condition. With MADD disrupting energy production, it could potentially exacerbate muscle weakness and hip joint instability. Coupled with neuromuscular issues stemming from CMT and NMDH, the MADD could contribute to the progression of hip dysplasia (Fig. 6).

Conclusions

This case reflects the complexity of hip dysplasia, particularly when coexisting with neuromuscular and metabolic disorders, emphasizing the need for ongoing research to gain a greater understanding. Developing more targeted therapeutic strategies,

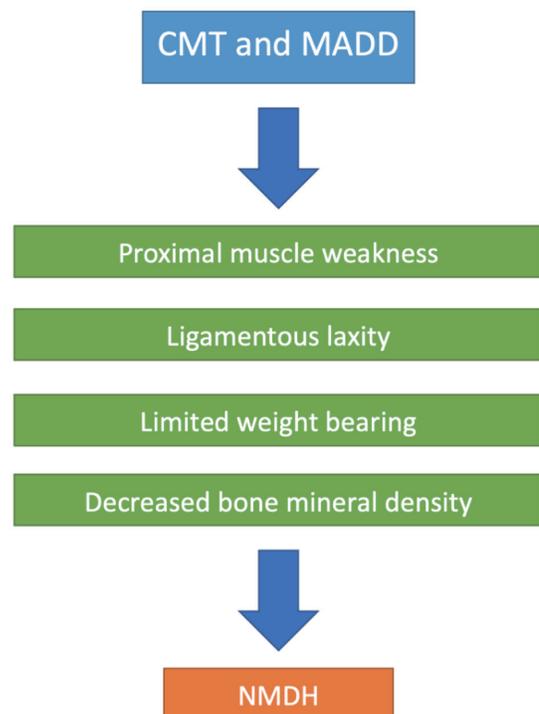


Figure 6. Suggested schematic representation of key abnormalities shared by Charcot-Marie-Tooth disease (CMT) and multiple acyl-CoA dehydrogenation deficiency (MADD) that in part can contribute to NMDH.

improving diagnostic techniques, and enabling earlier intervention are crucial to improving the quality of life for patients with similar co-morbid conditions. Identifying specific risk factors or biomarkers may aid in early detection, allowing for timely intervention and potentially delaying, or preventing, invasive procedures such as total hip replacements, ultimately leading to better patient outcomes with fewer complications in later life.

Learning points

The coexistence of neuromuscular disorders like CMT and metabolic disorders like MADD can complicate the presentation, diagnosis, and treatment of conditions like hip dysplasia. Hence, physicians should consider these potential interactions when diagnosing and treating such patients.

For patients presenting with complex cases of hip dysplasia, a multidisciplinary approach is essential for comprehensive patient management. Engaging with experts from various fields, such as endocrinology, neurology, orthopedics, and psychology, can lead to a more precise diagnosis and effective treatment plan.

Timely intervention plays a critical role in managing hip dysplasia, especially in patients with concomitant conditions like CMT and MADD. In this case, the patient underwent labral repair with shelf osteotomy followed by a total hip replacement, highlighting the importance of a proactive approach to surgical intervention.

This case underscores the need for further research into the relationships between neuromuscular disorders, metabolic disorders, and conditions like hip dysplasia. Such understanding may pave the way for improved diagnostic techniques, personalized treatment approaches, and ultimately better patient outcomes.

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None to declare.

Conflict of Interest

None to declare.

Informed Consent

Informed consent has been obtained from the patient.

Author Contributions

Conception and design: MHA. Administrative support: all

authors. Provision of study materials or patients: all authors. Collection and assembly of data: MHA, CA, and AH. Data analysis and interpretations: all authors. Manuscript writing: all authors. Final approval of manuscript: all authors.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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