CASE REPORT

From Diabetes to Neuropathy: A Diagnostic Journey to Leigh Syndrome

Arya Behzadi, MD [1]; Pooya Poormehr, MD [1]; Hedyeh Saneifard, MD [1]; Marjan Shakiba, MD [1]

[1] Department of pediatric endocrinology and metabolism, Mofid children's hospital, Shahid Beheshti university of medical sciences, Tehran, Iran

Keywords:

Leigh syndrome
Diabetes
Neurological disorders
Mitochondrial disorders
Genetic testing

Received:
25-Aug-2024
Accepted:
25-Sep-2024
Published:
07-Jan-2025

ABSTRACT

Diabetes is one of the most common chronic disorders in the world, characterized by chronic hyperglycemia. Among the rare causes of diabetes, Leigh syndrome is a rare genetic mitochondrial disorder with unusual manifestations like neurological deficits in addition to typical diabetes symptoms. This report enlightens others about the unusual presentation of diabetes in a pediatric population.

The studied case is a 6-year-old girl with hypothyroidism and diabetes. Post-SARS-CoV-2 infection, she developed progressive lower limb weakness. Magnetic resonance imaging (MRI) and electromyography-nerve conduction velocity (EMG-NCV) revealed brain lesions and polyneuropathy. Genetic testing using whole exome and Sanger sequencing confirmed mitochondrial gene mutations in the MT-NDI location, diagnosing her with Leigh syndrome.

Pediatric diabetic patients typically present with Type 1 diabetes mellitus (T1DM) or Type 2 diabetes mellitus (T2DM), but other causes must be considered. Leigh syndrome can manifest with neurological symptoms, requiring clinicians to recognize its diverse presentations for proper management.

This case highlights the importance of considering rare etiologies for diabetes to improve the prognosis and quality of life.

Introduction

Diabetes ranks as the second most common chronic disorder among children. In most populations, Type 1 diabetes mellitus (T1DM), characterized by an absolute insulin deficiency, is the predominant form, accounting for approximately 90% of cases. Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Diabetes in children usually presents with characteristic symptoms such as polyuria, polydipsia, and weight loss in association with glycosuria or ketonuria (1). Several pathogenic processes are involved in the development

How to cite this article: Behzadi A, Poormehr P, Saneifard H, Shakiba M. From Diabetes to Neuropathy: A Diagnostic Journey to Leigh Syndrome. Iran J Child Neurol. 2025; 19(1): 113-119. https://doi.org/10.22037/ijcn.v19i1.46085

*Corresponding Author: Saneifard H, MD. Department of Pediatric Endocrinology and Metabolism, Mofid children's Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran. Email: H.Saneifard@sbmu.ac.ir

of diabetes. These range from autoimmune destruction of the β-cells of the pancreas with consequent insulin deficiency to abnormalities resulting in insulin action resistance. The basis of the abnormalities in carbohydrate, fat, and protein metabolism in diabetes is the deficient action of insulin on target tissues (2). DM encompasses various types, each with unique characteristics despite sharing similar symptoms. Type 1 diabetes mellitus (T1DM) is caused by insufficient insulin secretion, while Type 2 diabetes mellitus (T2DM) results from insulin resistance. Besides, monogenic forms exist, such as maturity-onset diabetes of the young (MODY), including six different types. Additionally, neonatal diabetes mellitus (NDM) and mitochondrial diabetes exist, with the latter presenting a wide range of symptoms, from neurodevelopmental disorders to nonspecific findings or diabetic ketoacidosis (DKA) in the context of mitochondrial disease. Other conditions associated with INSR gene mutations include Leprechaunism (OMIM 246200), Wolfram syndrome, Alström syndrome, and Bardet-Biedl syndrome. In addition, various other factors can contribute to health issues, such as diseases affecting the exocrine pancreas. These include pancreas agenesis, pancreatectomy, cystic fibrosis-related diabetes, and hemochromatosis. Drugs or chemicals also induce conditions. Other endocrine diseases like Cushing syndrome, acromegaly, hyperthyroidism, and glucagonoma can also play a role. Rare diseases such as Progeria may present with non-specific symptoms, including signs of acromegaly, Cushing syndrome, and the like. Furthermore, Leigh syndrome is characterized by progressive neurological impairment. Abnormalities in tone, power, reflexes, coordination, bulbar function, seizures, extrapyramidal features, ocular dysmotility, neuropathy, and myopathy: imaging in these patients shows bilateral necrosis of the basal ganglia and brainstem structures. Cardiac, gastrointestinal, and renal dysfunction may also arise in this syndrome. Episodic decomposition, including brainstem dysfunction and central respiratory failure, in the context of infection or other stressors, can develop in both children and adults, leading to a stepwise deterioration (4). The following case report sheds light on Leigh syndrome as a rare manifestation of mitochondrial diabetes in a 6-year-old patient referred to Mofid Children's Hospital, Tehran, Iran, with DM.

Case Description:

The patient was a 6-year-old girl with a prior history of hypothyroidism who presented with symptoms of diabetes like polyuria and polydipsia, which prompted us to diagnose T1DM. Two years later, she was admitted to Mofid Children's Hospital due to lower limb weakness after being infected with SARS-CoV-2. At this admission, she complained of the exacerbation of her lower limbs' weakness since she was infected by SARS-CoV-2 three weeks before. Furthermore, her mother reported that her attention and concentration in preschool had decreased. She mentioned experiencing memory issues, occasionally walking awkwardly, having a seizure at home, and sometimes feeling drowsy. She had no complaints of nausea, vomiting, fever, cough, dyspnea, urine incontinence or retention. She was under treatment with insulin, glargine, and aspart for her diabetes and levothyroxine 25 micrograms daily for her hypothyroidism. No significant findings were observed in her familial, allergic, or habitual history; her height was almost 108 centimeters (Z score = -4.46), and she weighed around 19 kilograms (Z score = -1.88).

The most significant findings in her examination were reduced deep tendon reflexes, diminished force (3/5) in both lower limbs, short stature, and skin lesions due to psoriasis. No considerable findings were observed in the cardiopulmonary, abdominopelvic, head and neck, or skeletal systems. In addition to regulating blood sugar and hydration, this study approached Guillain-Barre syndrome due to ascending paraparesis manifesting consequently after SARS-CoV-2. Suspecting Guillain-Barre syndrome and autoimmune diabetes, we ordered thorough blood biochemistry tests, pancreatic islet-related autoantibodies, including insulin autoantibody (IAA), glutamic acid decarboxylase (GAD) antibody, and islet antigen-2 (IA-2) antibody to rule out autoimmune diabetes in the studied patient. SARS-CoV-2 PCR was conducted for the studied patient in addition to being vigilant of central neurological diseases using brain MRI and lumbar puncture. Subsequent to having expected results of pancreatic islet-related autoantibodies, She underwent treatment with IVIG for four consecutive days, and her brain MRI reported a bilateral non-enhancing multifocal confluent subcortical white matter lesion dominantly at the frontotemporal lobe about the impression of neuroimmune disorder like anti-MOG, NMSOD, as well as vasculitis-associated disease (i.e., SLE) should be considered in the DDX (Figure 1. After showing no improvement in her symptoms and chronicity, we requested an EMG-NCV, indicating moderate to severe and non-uniform demyelinating sensorimotor polyneuropathy in all limbs with secondary axonal loss and no evidence of myopathy or motor neuron disease at that time (Figure 2). Through further investigation using genetic assessment and whole exome sequencing (the WES test, confirmed by Sanger sequencing), it was clarified that some mitochondrial deficiencies were associated with Leigh syndrome (Figure 3). The researchers administered a mixture of coenzyme q10 and biotin to supplement with the fundamental drugs for mitigating the symptoms of diabetes in the examined patient (glargine, aspart insulin, and levothyroxine). Our new treatment regimen has proven to be significantly more effective than the previous one.

Discussion

In this case, we encountered an 8-year-old girl who had been exhibiting diabetes symptoms for two years before her hospital admission. Unexpectedly, she began to show signs of progressive motor weakness, urticaria, and ophthalmologic problems. Despite controlling her blood sugar, the neurological signs persisted. Consequently, we considered Guillain-Barre syndrome. However, the patient's condition did not improve using IVIG, leading us to conduct a genetic test. The results revealed that the patient was suffering from a rare mitochondrial disease known as Leigh's syndrome. Numerous metabolic diseases, including defects in carbohydrate, fat, and protein metabolism and defects in insulin secretion or action, can contribute to diabetes. These can manifest with symptoms such as glycosuria, ketonuria, fatigue, weakness, nausea, vomiting, weight loss, polydipsia, and polyuria (1, 3), the first complaints of the studied patients. Although the majority of pediatric diabetes cases are classified as Type 1 (1), it is crucial to acknowledge the existence of other diabetes types. These include Type 2 diabetes, neonatal diabetes (arises within the first three months of life), mitochondrial diabetes (typically associated with sensorineural deafness but in this instance

resulted in considerable motor weakness), cystic fibrosis-related diabetes, post-transplantation diabetes (often attributed to the administration of high-dose steroids and tacrolimus), stress hyperglycemia resulting from acute illness or injury, and MODY, representing approximately 0.2 to 0.5 percent of pediatric diabetes cases. Conditions that should prompt consideration of other types of diabetes include a familial history of diabetes with autosomal dominant inheritance, neurological findings involving the optic nerve and eighth nerve, significant insulin resistance, and a positive drug history of drugs known to be toxic to beta cells. Specific mitochondrial DNA mutations are associated with diabetes (1), the most common of which is the a3243G mutation in the DNA-encoded tRNA gene. Therefore, it is crucial to recognize the rare etiologies contributing to diabetes. Although some causes of diabetes are well-known, additional research is needed to investigate the rare conditions that can lead to the disease. In this case, despite regulating blood sugar, the neurological signs persisted. Due to the patient's upper respiratory infection symptoms before her hospital admission, we considered Guillain-Barre syndrome. Despite efforts, the symptoms continued unabated, and a detailed genetic analysis subsequently indicated a deficit in the patient's mitochondrial genome. This deficit correlates with a rare syndrome known as Leigh's syndrome, a rare inherited neurometabolic disorder that can cause subacute necrotizing encephalomyelopathy, which has autosomal recessive, X-linked, and mitochondrial patterns of inheritance (5). This syndrome manifests with various neurological and psychomotor characteristics, including muscular hypotonia, brainstem-related signs (such as strabismus, nystagmus, and swallowing difficulties), in addition to ataxia, pyramidal signs, seizures, and regression of psychomotor skills diagnosed by neurological and motor findings, raised lactate levels, and characteristic symmetric lesions in the brain stem or basal ganglia (5). There has been a report of a 2-year-old patient who was presented with insulin-dependent diabetes and progressive motor abnormalities, which were similar to ours. The MRI of that patient's brain (T2 and DWI) showed high signal lesions in the subcortical white matter. Later genetic testing on the patient uncovered that he was also experiencing mitochondrial dysfunction. However, some differences were found between the studied cases regarding the specific mutated gene (MT-NDI in our patient vs. 7117-13994 in theirs) and clinical manifestations (progressive lower limb weakness and hypothyroidism in our case vs. hearing disability, ptosis, external ophthalmoplegia, and retinitis pigmentosa at six years and six months in theirs) (6).

Compared to a meta-analysis by Chang et al., the present case was a 6-year-old girl with a history of hypothyroidism and T1DM who presented with lower limb weakness after SARS-CoV-2 infection and was subsequently diagnosed with Leigh syndrome due to an MT-NDI mutation. This is in contrast to the meta-analysis by Chang et al. (2020) regarding age at disease onset before the age of 2 years. This suggests a possible trigger or exacerbation of mitochondrial dysfunction by SARS-CoV-2 in our patient, which is not commonly documented in earlier-onset cases. Furthermore, the initial clinical features of our case, including lower limb weakness and MRI findings indicative of a neuroimmune disorder, differ from the results found in the meta-analysis, in which seizures, feeding difficulties, ocular abnormalities, fatigue, and ataxia were more

prevalent in the early stages of the disease. However, during the disease course, our patient's chronic lower limb weakness and demyelinating sensorimotor polyneuropathy were similar to what the meta-analysis found: developmental delay (57%), hypotonia (42%), respiratory dysfunction (34%), seizures (33%), poor feeding (29%), and weakness (27%). Regarding radiology, the examined patient showed bilateral non-enhancing multifocal confluent subcortical white matter lesions. Likewise, in the metanalysis, the most prominent neuroimaging finding was the involvement of the brainstem, midbrain, thalamus, cerebellum, and white matter. Genetically, the studied patient's MT-NDI mutation is close to the meta-analysis by Chang et al., finding that 32% of patients had mtDNA mutations, with the MT-ND and MT-ATP6 genes being the defective genes. This genetic resemblance highlights the importance of mtDNA mutations in the pathology of Leigh syndrome. This demonstrates the necessity of genetic testing in suspected cases (7). A study by Ramakrishna et al. revealed some similarities between the present results. Both of them were young patients with early-onset diabetes (six years old in our patient was the time of disease onset, and their case was nine years old) and multi-system involvement, indicating the complicated characteristics of mitochondrial disorders. Moreover, both of them had progressive symptoms, neurological complications, and short stature when they were first examined, and the diagnosis in both of them was confirmed by genetic testing. However, the cases also have fundamental differences. The current case had a history of hypothyroidism and experienced neurological symptoms after a viral infection, leading to a Leigh syndrome diagnosis. In contrast, their case is about a male initially presenting with short stature followed by gastrointestinal symptoms, hearing loss, and muscle cramps linked to the A3243G mitochondrial mutation. The discrepancy between the two cases' symptoms and genetic structure suggests that there might be multiple phenotypes of mitochondrial diabetes depending on the underlying affected gene. Besides, their case included a family history of diabetes and Wolf-Parkinson-White (WPW) syndrome in a sibling, while our case had no considerable familial history. Treatment responses exhibited differences; in our case, the patients derived advantages from vitamin E-levocarnitine, coenzyme Q10, and biotin (8).

Mitochondrial respiratory chain complex I is an essential component of the oxidative respiratory chain, with the mitochondrially encoded NADH: ubiquinone oxidoreductase core subunit 1 (MT-NDI) being one of the core subunits. The variation and content of MT-NDI can be used for disease diagnosis. Though historically, the treatment for LS has been largely supportive, new treatments are on the horizon. Treatment goals revolve around replenishing glutathione stores, reducing oxidative stress, and restoring oxidative phosphorylation. Some of the options proposed for the treatment of patients with Leigh syndrome include cysteamine.

Bitartrate was discontinued due to its lack of effectiveness. The agent KH176 was found to be well-tolerated, but it caused QTc prolongation and changes in T-wave morphology at higher doses. Biotin and thiamine supplementation led to clinical and radiological improvements in two siblings with missense mutations in the SLC19A gene, showing positive results with both biotin monotherapy and combination therapy. Coenzyme Q10 (CoQ10) is essential for oxidative phosphorylation in mitochondria.

Additionally, patients with renal abnormalities were diagnosed. However, clinical deterioration occurs if patients are already in the late stages of the disease before treatment initiation. Riboflavin reported improvements in patients with ACAD9 mutations. Carnitine, playing a role in fatty acid oxidation, and NAC, bypassing the electron transport chain, have been linked to decreased seizure frequency. Additionally, there have been reports of neurological improvements and reductions in acrocyanosis and petechiae in patients with mutations in ETHE1. In cases involving SLC39A8 mutations, uridine, and galactose have been found to enhance transferrin glycosylation patterns. Protein and valine-restricted diets have been beneficial for patients with valine-degradation issues, such as those with HIBCH and ECSH mutations. Furthermore, ketogenic diets can help manage the accumulation of toxic metabolites like methacrylic-CoA and acryloyl-CoA. However, the ketogenic diet can induce metabolic acidosis and lead to clinical deterioration in LS (9). MicroRNAs (miRNAs) are another treatment option suggested for Leigh syndrome. It can synergistically cooperate with the Argonaut 2 protein (Ago 2) to upregulate MT-NDI expression. This process compensates for the defective gene, resulting in the rescue of some energy production defects in the cells (10). Regarding radiographic features, measurable radiological features such as basal ganglia lesions and hexamethyl propylene oxime (HMPAO) on SPECT are associated with clinical improvement in LS and could serve as potential therapeutic biomarkers (9). The novelty of our case lies in the rare mitochondrial disease as the etiology of diabetes and the rare manifestation of Leigh's syndrome as diabetes. We suggest clinicians consider rare situations like mitochondrial diseases as the cause of diabetes, in addition to more common situations like Type 1 diabetes.

In Conclusion

This case highlights the importance of considering rare mitochondrial diseases, such as Leigh's syndrome, in the differential diagnosis of diabetes, especially when accompanied by neurological symptoms unresponsive to conventional treatments. The diagnosis of Leigh's syndrome, confirmed through genetic testing, underscores the value of a thorough evaluation in complex cases. The association between mitochondrial mutations and diabetes emphasizes the need for heightened awareness among clinicians to explore atypical etiologies beyond common forms like type 1 diabetes. Early identification and targeted management, including supportive therapies and emerging treatment options, may improve outcomes in these challenging cases. This case contributes to the growing body of evidence linking mitochondrial dysfunction to multi-systemic manifestations, broadening the understanding of its phenotypic diversity.

Acknowledgment

The Institutional Ethics Committee of Shahid Beheshti University of Medical Sciences gave ethical approval for this case report.

Patient Consent

Informed consent was obtained from the patient's legal guardian for the publication of this case report and any accompanying images.

Availability of Data and Material

Data supporting the results reported in this article are available from the corresponding author upon reasonable request.

Authors' Contribution

Arya Behzadi and Pooya Poormehr: Conducted the case study, gathered data, and contributed to interpreting the results. They also contributed to the work's conduct and reporting and prepared the manuscript. Marjan Hanifeh: Assisted in manuscript preparation and contributed to the literature review. Marjan Shakiba: Provided critical revisions, guided the study design, and oversaw the entire project. Hedyeh Saneifard: Planned the study, accepted full responsibility for the work and the conduct of the study, had access to the data, and controlled the decision to publish.

Conflict of Interest

The authors declared no conflict of interest.

References

1. Craig ME, Hattersley A, Donaghue KC. Definition, epidemiology and classification of diabetes in children and adolescents. Pediatr Diabetes. 2009;10(SUPPL. 12):3–12.
2. Diagnosis and classification of diabetes mellitus. Vol. 36, Diabetes Care. 2013.
3. Pucci M, Benati M, Lo Cascio C, Montagnana M, Lippi G. The challenges of diagnosing diabetes in childhood. Diagnosis. 2021;8(3):310–6.
4. Watson-Fargie T, Marshall V, Fullerton NE, Leach V, Pilz D, Hemingbrough CVY, et al. Leigh syndrome: an adult presentation of a paediatric disease. Pract Neurol. 2023 Aug 11;24(1):45–50.
5. Yadav AS, Mutanabbi M, Kundu GK, Kawser C. Leigh Syndrome: A Rare Mitrochondrial Disorder. Bangladesh J Child Heal. 2018;41(3):189–92.
6. Nemoto K, Sano K, Sato S, Maeda Y, Murayama K, Takanashi J ichi. A child with mitochondrial DNA deletion presenting diabetes mellitus as an initial. Radiol Case Reports [Internet]. 2022;17(9):2915–8. Available from: https://doi.org/10.1016/j.radcr.2022.05.061
7. Chang X, Wu Y, Zhou J, Meng H, Zhang W, Guo J. A meta-analysis and systematic review of Leigh syndrome: Clinical manifestations, respiratory chain enzyme complex deficiency, and gene mutations. Med (United States). 2020;99(5):E18634.
8. Ramakrishna MP, Pavithran P V., Bhavani N, Kumar H, Nair V, Menon AS, et al. Mitochondrial Diabetes: More Than Just Hyperglycemia. Clin Diabetes. 2019;37(3):298–301.
9. Tiet MY, Lin Z, Gao F, Jennings MJ, Horvath R. Targeted Therapies for Leigh Syndrome: Systematic Review and Steps towards a "Treatabolome." J Neuromuscul Dis. 2021;8(6):885-97.
10. Lin X, Zhou Y, Xue L. Mitochondrial complex I subunit MT-ND1 mutations affect disease progression. Heliyon [Internet]. 2024;10(7):e28808. Available from: https://doi.org/10.1016/j.heliyon.2024.e28808