

MICROCEPHALY, EPILEPSY, AND DIABETES SYNDROME 1: A MOROCCAN CASE REPORT OF NOVEL COMPOUND HETEROZYGOUS *IER3IP1* MUTATIONS AND LITERATURE REVIEW

Jelti H^{1,2*}, Khabbache K^{3,4}, Bouressas S^{1,2}, Hacht F^{1,2}, Oulmaati A^{3,4}, Lamzouri A^{1,2}

***Corresponding Author:** Jelti Houda, PhD, Department of Medical Genetics and Oncogenetics, Mohammed VI University Hospital center, Route de Rabat Km 17 BP 398, Gzenaya, Tangier, Morocco, Phone Number: +212650644705, Email Address: houda.jelti@etu.uae.ac.ma

ABSTRACT

Microcephaly, Epilepsy, and Diabetes Syndrome 1 (MEDS1) is a very rare autosomal recessive neurodevelopmental disorder (OMIM#614231) characterized by the triad microcephaly with simplified gyration, neonatal permanent diabetes and infantile epileptic encephalopathy. Its occurrence is due to biallelic mutations in the *IER3IP1* gene, which encodes for the Immediate Early Response 3 Interacting Protein 1 (IER3IP1). To date, only eleven cases have been reported worldwide. Here, we describe the twelfth case from northern Morocco. This 4-month-old patient, born to a healthy non-consanguineous couple presented with microcephaly, epileptic seizures and insulin-requiring permanent neonatal diabetes. Brain MRI revealed simplified gyration with partial agenesis of the corpus callosum. Targeted next generation sequencing identified the patient as compound heterozygous for two *IER3IP1* variants; a novel nonsense mutation, p. Leu79Ter, and a previously reported pathogenic variant, p. Val21Gly. This report extends the phenotypic and genotypic spectrum of MEDS1 syndrome and provides further evidence of the role of IER3IP1 in neural and pancreatic development, emphasizing the clinical importance of genetic screening in cases of early-onset diabetes and epilepsy especially when accompanied by significant head growth failure in a newborn infant. Further research into the pathophysiol-

ogy of IER3IP1 may potentially lead to new therapeutic approaches.

Keywords: Epileptic encephalopathy, IER3IP1, MEDS1, Microcephaly, Neonatal diabetes, Neurodevelopmental disorder.

INTRODUCTION

Microcephaly, Epilepsy, and Diabetes Syndrome 1 (OMIM number: 614231), also called MEDS1 syndrome is a rare autosomal recessive neurodevelopmental disorder. The key criterion for the diagnosis of MEDS1 is the triad microcephaly with simplified gyration, neonatal permanent diabetes and infantile epileptic encephalopathy [1]. This disorder is caused by biallelic mutations in Immediate Early Response 3 Interacting Protein 1 gene (*IER3IP1*), located on chromosome 18q21.1. IER3IP1 plays a crucial role in the homeostasis of the endoplasmic reticulum (ER), particularly in neuronal and pancreatic beta-cell functions[2]. Pathogenic mutations in this gene have been associated with early neuronal apoptosis and disturbed beta-cell maturation which explains the neurodevelopmental and diabetic manifestations of MEDS1[3].

Typical clinical presentation of this condition includes a severe developmental delay, refractory seizures, early onset diabetes, dysmorphic features and recurrent infections. Other anomalies such as abnormal genitalia and skeletal defects have also been reported [4–6]. The majority of cases survive only to early childhood. The rarity and the difficult management of the disease, underscores the importance of comprehensive phenotype-genotype characterization of each case, which helps deepen our understanding of the pathophysiology of the syndrome and may improve diagnostic and therapeutic approaches.

To date, only eleven cases have been reported worldwide, mainly from the Middle East and North Africa with most involving consanguineous families. Here, we present

¹ Department of Medical Genetics and Oncogenetics, Mohammed VI University Hospital center, Tangier, Morocco

² Life and Health Sciences Laboratory, Faculty of Medicine and Pharmacy of Tangier, Abdelmalek Assaadi University, Morocco

³ Department of pediatrics, Mohammed VI University Hospital center, Tangier, Morocco

⁴ Faculty of Medicine and Pharmacy of Tangier, Abdelmalek Assaadi University, Morocco

an additional case of a patient, a 4-month-old Moroccan child, who is compound heterozygous with two different variants in *IER3IP1* gene, one of which is a novel variant. This report not only expands the genotypic spectrum of MEDS1 but also represents the first known case from northern Morocco. Our findings contribute to the growing body of MEDS1, especially as far as the observed phenotypic variability and the impact on genetic counselling in affected families is concerned.

MATERIALS AND METHODS

Clinical report

A 4-month-old male proband, first born child of a healthy non-consanguineous couple from northern Morocco (Figure 1), was referred to genetics clinical counseling for associated microcephaly, epilepsy and neonatal diabetes. At the time of delivery, his father and his mother were aged 38 and 28 years, respectively. There are no reported other cases within the family. The pregnancy proceeded without complications, but the delivery, occurring at term vaginally, was complicated by perinatal asphyxia. Birth weight was approximately 3,000 g. Although his weight and length were within normal ranges, his head circumference was markedly reduced (-4 SD).

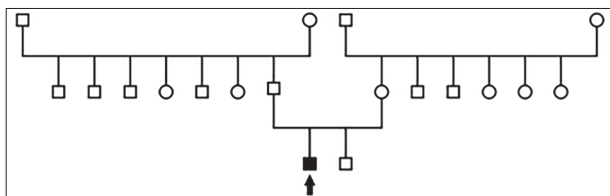


Figure 1. Family pedigree.

At one month of age, the patient developed partial seizures on the right side, characterized by myoclonic episodes resistant to anti-epileptic initial treatment and leading to multiple hospitalizations. An electroencephalogram (EEG) performed showed a discontinuous background activity and frontal sharp waves, consistent with delayed maturation. A second EEG performed two months later, recorded frequent left centrottemporal seizures spreading toward the occipital region, with episodes marked by fixed gazes and focal seizures. Anti-seizure therapy was initiated with phenobarbital and levetiracetam. Due to poor seizure control, doses were increased and clobazam was later added. Despite this combination therapy, the patient continued to experience frequent partial seizures and myoclonic episodes. The response to treatment remained partial.

Brain MRI revealed a diffuse simplified gyral pattern (lissencephaly type 1), predominantly frontal and occipital

bilaterally, associated with partial agenesis of the corpus callosum and moderate ventriculomegaly (Figure 2). At three months of age, the patient developed insulin-requiring permanent neonatal diabetes with elevated blood glucose level between 5.5 and 6.1 g/L and HbA1c at 12 % measured during his hospitalization. The insulin therapy was initiated. Management was complicated by frequent hypoglycemic episodes, requiring adjustment of insulin doses and nutritional support.

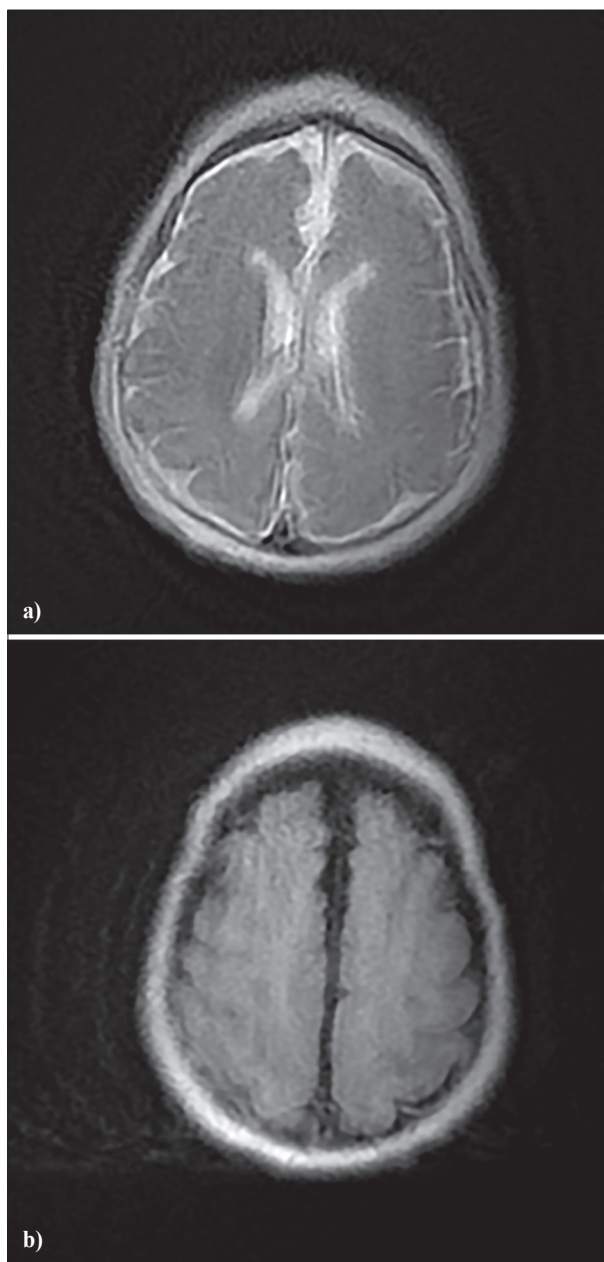


Figure 2. Brain MRI of the patient
(a) Axial T2-image showing partial agenesis of the corpus callosum with moderate ventriculomegaly.
(b) Axial FLAIR image showing a simplified gyral pattern consistent with lissencephaly.

Laboratory tests revealed blood amino acid, cerebrospinal fluid (CSF) amino acid, acyl-carnitine, and urine organic acid levels within normal limit.

Clinical examination revealed hypotonia, severe developmental delay and dysmorphic features, including short forehead with bitemporal grooving, bulbous nose, full and ruddy cheeks, deep philtrum, small mouth with tented vermilion of upper lip, micrognathia, prominent ears and a short neck (Figure 3). No skeletal defects or genitalia abnormalities were detected in our patient. Recurrent pneumonia infections complicated the clinical course leading to the patient's death at 1 year and 3 months.



Figure 3. Clinical features of the patient.

Genetic testing

Written informed parental consent was obtained and the patient's identity has been anonymized to maintain confidentiality. DNA was extracted from peripheral blood collected from the proband and his parents. Sequencing analysis for all known neonatal diabetes etiological genes was performed using a custom-designed targeted next generation sequencing assay (Twist Bioscience Custom v5.4 / Illumina NextSeq500/550)[7].

This assay analyzes the coding regions and conserved splice sites of 45 nuclear genes associated with monogenic forms of neonatal and syndromic diabetes, including *IER3IP1*, and is also capable of detecting copy number variations. The list of targeted genes is available at: <https://www.diabetesgenes.org/tests->

[for-diabetes-subtypes/targeted-next-generation-sequencing-analysis-of-45-monogenic-diabetes-genes/](#). Mitochondrial DNA variants were not analyzed in this panel.

Variant classification was performed using the ACMG guidelines. The identified variants were confirmed by Sanger sequencing in the proband and both parents.

RESULTS

The patient was identified as compound heterozygous for two *IER3IP1* variants:

NM_016097.5: c.62T>G p.(Val21Gly)

NM_016097.5:c.236T>G p.(Leu79Ter)

The *IER3IP1* missense variant p. Val21Gly, presumed to result in a protein with altered function, is classified as pathogenic and has been previously reported (Table 1).

To our knowledge, the nonsense variant p. Leu79Ter has not been previously reported in any literature reports or in the healthy population database (gnomAD). However, in silico prediction using Mutation Taster stated the variation as “deleterious”. The p. Leu79Ter variant results in a premature stop-codon predicted to produce a truncated protein lacking less than 10% of the full protein. According to The American College of Medical Genetics (ACMG) 2020 criteria, the variant c.236T>G p. Leu79Ter in *IER3IP1* is classified as “likely pathogenic” (PVS1+PM2+PM3+PP4).

Segregation analysis revealed that the mother was heterozygous for the first variant, and the father for the second one.

DISCUSSION

To the best of our knowledge, this study presents the first documented case of MEDS1 syndrome from northern Morocco, constituting the twelfth case worldwide and the third case with compound heterozygous mutations in *IER3IP1* gene. This report enhances the understanding of MEDS1 syndrome by illustrating its clinical and genetic diversity.

First described in 2011 by Poulton et al, Microcephaly, epilepsy, and diabetes syndrome 1 (MEDS1) is a neurodevelopmental disorder characterized by a triad of microcephaly, a simplified gyral pattern on brain MRI, infantile-onset severe epilepsy and neonatal diabetes [1]. This autosomal recessive disorder is known to result from biallelic mutations in the *IER3IP1* gene either in homozygous or compound heterozygous state.

Compared to other MEDS1 cases, our patient shares a similar clinical presentation with most of reported cases. The early onset of epilepsy and diabetes observed in our patient is consistent with most cases (Tab1). Only a single

Table 1. Clinical and Genetic Findings in Reported MEDS1 Cases and Current Case

Article	Poulton et al 2011		Abdeslam et al 2012				Shalev et al 2013	Valenzuela et al 2017	Rjiba et al 2021	Söbü et al 2022	Zegarra et al 2023	Current report
Case	1	2	3	4	5	6	7	8	9	10	11	12
Parental origin	Morocco	Argentina	Egypt	Egypt	Egypt	Egypt	Libya- Tangier Colombia	Spain	Tunisia	Turkey	NR	Northern Morocco
Consanguinity	+	Presumed	+	+	+	+	-	-	+	+	-	-
Sex	M	M	M	F	F	F	M	M	M	M	F	M
Diabetes onset	2 mo	At birth	<1 wk	2 mo	40 days	2 wk	2 mo	5 wk	2 mo	18 mo	4 mo	3 mo
Epilepsy onset	2 mo	2 mo	Few days of life	2 mo	At birth	2 mo	2 mo	NR	2 mo	2 mo	2 mo	1 mo
Microcephaly	+	+	+	+	+	+	+	+	+	+	+	+
Dysmorphic features	NR	NR	+	+	+	+	+	+	+	+	NR	+
Skeletal manifestations	NR	NR	+	+	+	+	NR	-	-	NR	NR	-
Abnormal genitalia	Hypogonadism	-	-	-	-	-	Retractile testes/normal genitalia	-	Small genitalia/unilateral cryptorchidism	-	-	-
Age of death	1 y 5 mo	2 y 3 mo	5 y 5 mo	2 y 3 mo	3 y 5 mo	NR	8 y	7 weeks	1 y	NR	NR	1 y 3 mo
IER3IP1 Variants	p.Val21Gly	p.Leu78Pro	p.Leu78Pro	p.Leu78Pro	p.Leu78Pro	p.Leu78Pro	p.Val21Gly) /p.phe27fsSer*25	p.Leu78Pro	p.Val21Gly	p.Ala18Val	p.Leu80* /c.2T>A (initiator codon)	p.Val21Gly /p.Leu79Ter
Variant status	Homozygous	Homozygous	Homozygous	Homozygous	Homozygous	Homozygous	Compound heterozygous	Homozygous	Homozygous	Homozygous	Compound heterozygous	Compound heterozygous

NR: Not reported / Y: year / Mo: month / Wk: weeks

case from Turkey has been reported to have experienced diabetes onset later, at 18 months old [8], suggesting the possibility that the variant found in this case (p.Ala18Val), which has not been reported in other cases, may have a less severe effect on protein function. Furthermore, it is important to mention that similar dysmorphic features seen in our patient have been reported previously in other MEDS1 patients, including short forehead, bulbous nose, and micrognathia [4–6,8,9]. Skeletal defects, such as multiple epiphyseal dysplasia, have been reported in some cases [6]. In our case study, no skeletal abnormalities were observed. Some Cases reported abnormal external genitalia, including small genitalia and unilateral cryptorchidism [4], while others had retractile testes with normal genitalia [5] and hypogonadism [1], suggesting a possible link between *IER3IP1* variants and impaired male genital development. In contrast, our patient displayed no abnormal genitalia. The precise mechanism by which *IER3IP1* gene affects genital development remains unknown. Further research is recommended to understand the link between *IER3IP1* variants and genital development.

IER3IP1 encodes for immediate early response 3 interacting protein 1 (IER3IP1) which is a small conserved protein expressed across multiple species, including humans, mice, zebrafish, and yeast, with high expression in the developing brain cortex and pancreatic beta cells [1]. The Human *IER3IP1* gene, localized on human chromosome 18q21.1, comprises 3 exons that encodes an 82-amino acid protein. This protein contains 2 transmembrane domains and a putative G-patch domain [2]. IER3IP1 is located in the endoplasmic reticulum (ER) through its C-terminal transmembrane domain.

Pathogenic variants in *IER3IP1* gene disrupt endoplasmic reticulum (ER) function, leading to increased ER stress, impaired β -cell maturation, and increased neuronal apoptosis, which collectively contribute to the clinical manifestations of MEDS1, impacting both neuronal development and insulin production [3,10]. Loss of *IER3IP1* function in neurons can lead to significant changes in secreted and surface-localized proteins involved in neuronal development and migration, which may disrupt cellular homeostasis necessary for proper neuronal function [3]. In pancreatic beta cells, *IER3IP1* mutations result in impaired ER function, causing elevated ER stress and proinsulin trafficking, which ultimately leads to reduced beta cell number and increased apoptosis, contributing to insulin-deficient diabetes [11].

Our case introduces a novel nonsense variant p. Leu-79Ter not previously identified in any population database. This variant leads to a premature stop codon predicted to result in a truncated protein with a partial (10%) loss of functional domains. Additionally, the p.Val21Gly Variant,

found in our patient has been reported in other patients of North African origins, including Moroccan, Libyan-Tangier and Tunisian cases [1,4,5] suggesting it may be a rare ancestral variant rather than a recurrent hotspot mutation.

Currently, there are no targeted therapies for MEDS1, and treatment is limited to supportive care. Most cases died at an early age, often due to respiratory tract infections, with only one reported case surviving until the age of 8 [5]. This high early mortality rate proves the severity of the syndrome and the challenges in managing its complications. Zegarra et al [12] report a successful use of ketogenic diet to control both diabetes and seizures in an infant with MEDS1 but the long-term outcome of the patient remains unclear. This demonstrates the importance of close monitoring to prevent diabetic ketoacidosis.

Advances in understanding the genetic basis of MEDS1 may open pathways for future therapeutic strategies, such as gene therapy. Early genetic diagnosis is crucial for managing complications such as neonatal diabetes and for providing appropriate epilepsy care, potentially improving patient outcomes.

Our case highlights the importance of early genetic diagnosis for timely clinical management and family planning. Following the diagnosis and the unfortunate death of the patient at 15 months due to recurrent respiratory infections, genetic counselling was provided to the family.

Techniques such as preimplantation/ prenatal genetic diagnosis were explained to the parents. Despite limited resources, they decided to monitor their second pregnancy closely with frequent obstetric ultrasounds and opted for termination of pregnancy in case of suspicious findings. Currently the mother has given birth to a second child, who does not exhibit any symptoms of Meds1 syndrome.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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