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Short Communication

Transient neonatal renal failure and massive polyuria in MEGDEL syndrome

Carole Harbulot [a,1], Stéphanie Paquay [a,b,1], Imen Dorboz [c], Samia Pichard [a,b], Agnès Bourillon [d], Jean-François Benoist [d], Claude Jardel [e], Hélène Ogier de Baulny [a,b], Odile Boespflug-Tanguy [a,c], Manuel Schiff [a,b,c,*]

[a] Child Neurology, Hôpital Robert Debré, APHP, Paris, France
[b] Reference Center for Inborn Errors of Metabolism, Robert Debré University Hospital, APHP, Paris, France
[c] Inserm U1141 and Université Paris-Diderot, Sorbonne Paris Cité, site Robert Debré, Paris, France
[d] Biochemistry, Hôpital Robert Debré, APHP, Paris, France
[e] Biochemistry, Hôpital de la Salpêtrière, APHP, Paris, France

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ABSTRACT

Background: MEGDEL (3-methylglutaconic aciduria with deafness, encephalopathy, and Leigh-like syndrome) syndrome is a mitochondrial disorder associated with recessive mutations in *SERAC1*.
Objectives: To report transient neonatal renal findings in MEGDEL syndrome.
Results: This 7 year-old girl was the first child of consanguineous Turkish parents. She exhibited an acute neonatal deterioration with severe lactic acidosis and liver failure. Initial evaluation revealed massive polyuria and renal failure with 3-methylglutaconic aciduria. Symptoms and biological findings progressively improved with symptomatic treatment but lactic acidosis and high lactate to pyruvate ratio along with 3-methylglutaconic aciduria persisted. At 8 months of age, a subacute neurological degradation occurred with severe hypotonia, dystonia with extrapyramidal movements and failure to thrive. Brain MRI revealed basal ganglia lesions suggestive of Leigh syndrome. At 3 years of age, sensorineural deafness was documented. MEGDEL syndrome was further confirmed by the identification of an already reported homozygous mutation in *SERAC1*.
Conclusion: Transient neonatal polyuria and renal failure have not been reported to date in *SERAC1* defective patients. Such neonatal kidney findings expand the clinical spectrum of MEGDEL syndrome.

1. Introduction

MEGDEL (3-methylglutaconic aciduria with deafness, encephalopathy, and Leigh-like syndrome, MIM 614739) syndrome is a recessively inherited disorder recently associated with recessive mutations in *SERAC1* [1]. *SERAC1* (serine active site containing 1) is a protein involved in phosphatidylglycerol remodeling located in the mitochondrial-associated membrane at the contact site between endoplasmic reticulum and mitochondria. The identification of *SERAC1* mutations in MEGDEL syndrome helped defining a new category of nuclear-encoded mitochondrial-related diseases, namely genetic defects of phospholipid biosynthesis, remodeling and metabolism [2–6]. These diseases present a large spectrum of clinical consequences. Such new category of mitochondrial-related inborn errors of phospholipid metabolism became clearly identifiable with the recent application of next generation sequencing methodologies. These diseases include *TAZ* mutations (Barth syndrome), *DNAJC19* (DCMA syndrome), *SERAC1* mutations (MEGDEL syndrome), *AGK* mutations (Sengers syndrome), *DDHD1* and *DDHD2* mutations (hereditary spastic paraplegia). In *TAZ*, *SERAC1*, *DNAJC19* and *AGK* mutations, 3-methylglutaconic aciduria (3-MGA) is observed [3].

We report herein transient kidney features in a neonate later diagnosed with MEGDEL syndrome.

1.1. Case description

This first girl from consanguineous healthy Turkish parents was born at 39 weeks of gestation by caesarean section because of fetal bradycardia. Birth weight, height and head circumference were 2.200 kg, 45 cm, and 31 cm respectively, (<3rd percentile). Apgar score was 10/10.

At 20 h of life, she was admitted to the intensive care unit for respiratory failure and tachycardia along with truncal hypotonia and tremor. Labs showed metabolic acidosis with increased anion gap due to hyperlactatemia (19.8 mM, normal value <2.5 mM), moderately elevated ammonia level (186 μM, normal value <90 μM), moderately increased liver enzymes (1.5 fold) and CPK (1600 IU/L, normal value <800) and transient liver failure (protrombin time 29%, factor V 28%).

* Corresponding author at: Reference Center for Inborn Errors of Metabolism, Hôpital Robert Debré, 48 Bd Sérurier, 75935 Paris Cedex 19, France.
E-mail address: manuel.schiff@aphp.fr (M. Schiff).
[1] These authors contributed equally to this work.

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She also exhibited hypernatremic dehydration (there was a decrease of 140 g compared to birth weight and blood sodium was 150 mM, normal value <145 mM), renal failure with increased serum creatinine (95 μM, normal range 25–80 μM) and massive polyuria (maximum diuresis 15 mL/kg/h, normal range 2–5 mL/kg/h) with hyperlactaturia (lactate to creatinine ratio of 1.6 mmol/mmol, normal value <0.1). There was no sign of proximal tubular dysfunction. Urine osmolality was low (192 mOsm/kg; reference range: 500–800 mOsm/kg). Sustained urinary excretion of 3-MGA was noted but exact values could not be quantified due to elevated lactate excretion. Renal ultrasound was normal with no sign of acute tubular necrosis. Brain MRI was normal (not shown). Thanks to symptomatic intravenous compensation of urinary water losses (initial daily fluid intake: 225 mL/kg/day; sodium intake: 15 mEq/kg/day), renal abnormalities disappeared within 3 days.

From the age of 8 months, she exhibited failure to thrive along with head circumference growth arrest. Psychomotor milestones were delayed and truncal hypotonia with left eye strabismus were noted. At 15 months of age, her weight, height and head circumference were 7.250 kg (<−2.5 SD), 74.5 cm (<−0.5 SD) and 44.5 cm (<−2 SD) respectively. Clinical examination revealed axial hypotonia, with pyramidal signs, strabismus and left amblyopia associated with hypermetropia. Labs showed a 2-fold increase of liver enzymes and high lactate in blood (maximum in the fed state at 5.4 mM, normal value <2 mM) and cerebrospinal fluid (3.20 mM, normal <2 mM) with elevated CSF lactate to pyruvate ratio (16, normal <12). A second brain MRI disclosed symmetrical and bilateral hyperintensities in the caudate nuclei and putamina associated with cerebellar atrophy (reported in [7]). Such MRI findings together with subacute clinical deterioration were suggestive of Leigh syndrome. Urinary 3-MGA excretion persisted.

From 3 years of age, severe dystonia, spastic tetraparesis and hearing loss were noted. Audiometry revealed bilateral sensorineural deafness, which was severe on the right side and profound on the left side.

Speech development was absent and motor development milestones severely delayed but rigorous assessment of neurodevelopment could not be performed.

The patient is currently 7 years and 9 months old and exhibits a severe and slowly progressive dystonic encephalopathy with correct growth parameters (weight: −0.5 SD, height: 0 SD) due to improvement of the caloric intake. Renal function (as assessed by serum creatinine) is normal and there is no polyuria.

Mitochondrial respiratory chain activities were normal in skin fibroblasts and skeletal muscle (not shown). MEGDEL syndrome was suspected. Whole exome sequencing had been performed just before the identification of the molecular basis of MEGDEL syndrome (*i.e.* description of *SERAC1* mutations [1]) and found an already reported homozygous mutation in *SERAC1* [1]. This mutation (c.1822_1828 + 10del17ins9) was confirmed by Sanger sequencing with appropriate parental segregation.

2. Discussion

Clinical and neuroradiological [7] presentation of approximately 40 reported MEGDEL patients is relatively homogeneous. However, some additional, initially undescribed features were reported such as neonatal hepatopathy [8], optic nerve atrophy, microcephaly, and myoclonic epilepsy [9]. None of these additional findings included transient neonatal kidney dysfunction. None of the 3 reported patients harboring the same mutation than our patient exhibited similar neonatal kidney abnormalities [1]. However, unlike our patient, these 3 patients were not homozygous but compound heterozygous for this mutation. Therefore, no strict genotype-phenotype correlation can be made between these 3 patients and ours.

Accordingly, the data reported here suggest that such transient renal findings were not due to the severity of the clinical deterioration but could rather be probably ascribable to a specific defect related to *SERAC1* dysfunction in the neonatal kidney. More specifically, severe neonatal hypoxic ischemic conditions can show kidney damage usually expressed by acute tubular necrosis and not by massive polyuria. In keeping with this, the fact that exome sequencing did not identify any recessive mutation in other genes does not support the role for another recessive disorder at the origin of these kidney findings.

Most of the reported *SERAC1* patients exhibited defective respiratory chain activities in cultured skin fibroblasts and/or skeletal muscle, which was surprisingly not the case for our patient. The exact function of *SERAC1* has not been fully elucidated yet and the impact of *SERAC1* dysfunction on mitochondrial respiratory chain function has not been clarified. Interplay of *SERAC1* with intracellular cholesterol metabolism has been suggested as filipin testing showed abnormal results related to accumulation of intracellular unesterified cholesterol as observed in Niemann-Pick type C disease [1]. Such abnormal filipin testing was also observed in our patient (not shown).

Another unsolved issue concerns the role for 3-MGA urinary excretion in some of these mitochondrial defects of complex lipids biosynthesis and remodeling. To date, 3-MGA is definitely a biomarker for these defects [10] but its role in the pathophysiology of MEGDEL remains to be elucidated. 3-MGA could probably be viewed as a biomarker for inborn errors involving a disruption of the architecture of the mitochondrial membranes [3,11].

Renal disease may be observed in neonatal mitochondrial respiratory chain diseases that usually present with severe proximal tubular dysfunction or nephrotic syndrome [12] but transient water loss and kidney failure were not reported in neonatal mitochondrial diseases.

To conclude, massive polyuria with low urine osmolality and transient neonatal renal failure widens the spectrum and further delineates the phenotype of MEGDEL syndrome for which only 30 to 40 patients are known. In the setting of a neonatal deterioration with lactic acidosis and 3-MGA, such renal findings should be searched for and if present prompt the clinician to perform molecular analysis of *SERAC1*.

Compliance with ethics guidelines

Conflict of interest

Carole Harbulot declares that she has no conflict of interest.
Stéphanie Paquay declares that she has no conflict of interest.
Imen Dorboz declares that she has no conflict of interest.
Samia Pichard declares that she has no conflict of interest.
Agnès Bourillon declares that she has no conflict of interest.
Jean-François Benoist declares that he has no conflict of interest.
Claude Jardel declares that she has no conflict of interest.
Hélène Ogier de Baulny declares that she has no conflict of interest.
Odile Boespflug-Tanguy declares that she has no conflict of interest.
Manuel Schiff declares that he has no conflict of interest.

Informed consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

Details of the contributions of individual authors

Carole Harbulot analyzed the data and wrote the paper. Stéphanie Paquay analyzed the data and wrote the paper. Imen Dorboz performed molecular analysis. Samia Pichard drafted the manuscript. Agnès Bourillon performed molecular analysis. Jean-François Benoist drafted the manuscript. Claude Jardel performed respiratory chain analysis. Hélène Ogier de Baulny drafted the manuscript. Odile Boespflug-Tanguy drafted the manuscript. Manuel Schiff wrote the paper.

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