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***RMNDI* mutations in two siblings: severe renal hypoplasia but different levels of extrarenal abnormality severity: the ethics of decision making**

Short title: *RMNDI* and severe renal hypodysplasia

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Abstract

Mutations in the *RMND1* gene, causing defects in the mitochondrial respiratory chain, result in a very heterozygous phenotype. Currently there are 36 cases reported in the literature.

We report two siblings from a non-consanguineous family who were severely affected by a compound heterozygous *RMND1* mutation that had not been described previously and were treated differently for their end-stage renal disease. We summarize all previous published cases and focus on the importance of extrarenal comorbidities in the context of therapeutic decision making (renal replacement therapy) and its ethical relevance.

1. Introduction

Mutations in the *RMND1* gene, causing defects in the mitochondrial respiratory chain, result in a very heterogenic phenotype. In 2012, Janer et al. identified a homozygous missense mutation in the *RMND1* gene responsible for the phenotype of two siblings presenting with severe encephalopathy, lactic acidosis, and pharmacologically resistant seizures leading to an early fatal outcome [1]. In 2016, Yi Shiau Ng et al. reviewed all the previously described cases [2]; three additional cases were reported in 2017 [3]. All these cases were relatively similar. However, a phenotype resembling Perrault syndrome, namely a combination of sensorineural hearing loss, dysfunction, or missing ovaries and neurological problems, was recently reported to be also due to an *RMND1* mutation[4]. This brings the total of published pediatric cases to 36. In the adult population, the expression of *RMND1* is modified by breast cancer risk variants in estrogen-negative breast tumors [5].

We describe here two pediatric siblings affected by a compound heterozygous mutation in the *RMND1* gene, with a severe renal phenotype but heterogeneity in the severity of extrarenal manifestations, namely sensorineural deafness, bilateral temporal lobe cysts, failure to thrive, cardiac insufficiency, and developmental delay. Table 1 summarizes all previous published cases and our new two patients.

2. Observation

The first case is a boy who was born premature with normal birth weight for gestational age but microcephaly, strabismus, and severe hypotonia. Due to severe hypotonia, mechanical ventilation was required for 11 days. Bilateral sensorineural deafness was discovered at 9 months of age; 1 year later psychomotor developmental delay and growth retardation became obvious. Cerebral MRI at the age of 15 months demonstrated white matter abnormalities and a right temporal lobe cyst. Sitting was obtained at the age of 18 months,

walking at the age of 3 years and riding a three-wheeler at the age of 5 years. He learned sign language. Echocardiography was performed at the age of 4 years and was normal. During follow-up for weight loss at the age of 7, chronic kidney disease (CKD) with sodium wasting was discovered (eGFR 36 mL/min per 1.73 m²). Renal ultrasounds showed bilateral hyperechoic hypoplastic kidneys. The boy developed arterial hypertension. Metabolic assessment showed hyperlactatemia in both serum and cerebrospinal fluid. Cerebral MRI found white matter abnormalities in the frontotemporal area, with a T2 hypersignal corresponding to leukodystrophy. Growth hormone treatment was started in 2010. Despite close follow-up, the boy developed hypertensive retinopathy requiring a combination of four antihypertensive drugs. At the age of 11, echocardiography showed a moderate left ventricle hypertrophy, that was completely normal 2 years later. However, renal function gradually worsened, requiring renal replacement therapy (RRT) for end-stage renal disease (ESRD) at the age of 13 and 11 months later a subsequent renal transplantation. At the age of 17, post-transplant progression was uneventful, graft function was normal (iohexol clearance 98 mL/min per 1.73 m²), and the boy was attending adapted schooling. Eventually, a mutation in the *RMND1* gene (compound heterozygous NM_017909.2:c.533C>T, p.Thr178Met and NM_017909.2:c.713A>G, p.Asn238Ser) was found.

The second case is the first case's sister. She was born premature with a normal birth weight for gestational age and no overt microcephaly. She presented with respiratory insufficiency requiring surfactant and mechanical ventilation for 3 days. At the age of 3 months, she presented with a severe gastroesophageal reflux treated symptomatically; at that time, systematic renal screening was performed, showing two relatively small kidneys (44 and 46 mm for a height of 51 cm and thus an estimated size of 54 mm), normal blood pressure and slightly decreased renal function (creatinine 43 µmol/L). During the first year, she developed psychomotor delay, growth retardation (−3 SD), axial hypotonia, bilateral strabismus, and

sensorineural deafness. Creatinine progressively increased, with bilateral hypoplasia confirmed during follow-up and requiring sodium supplementation. At the age of 3 years, cerebral MRI showed hypoplasia of the corpus callosum, bilateral temporal lobe cysts, and white matter abnormalities corresponding to leukodystrophy. Metabolic evaluation revealed hyperlactatemia in serum as well as in cerebrospinal fluid. At the age of 5, the girl developed hypertension treated by amlodipine, further requiring the addition of acebutolol. At the age of 9, she was admitted to the PICU for an episode of severe pulmonary edema, severe cardiac insufficiency (shortening fraction left ventricle, 15%) and ESRD. Despite therapeutic optimization, cardiac function never recovered, and a multidisciplinary evaluation was undertaken. Given the severity of the cardiac impairment and its incurability in a context of severe psychomotor delay and encephalopathy, it was decided not to initiate RRT but rather to propose palliative support. She developed peripheral hypothyroidism at 9.9 years and she eventually died at the age of 10 years. The same compound heterozygous *RMND1* mutation was found. DNA testing of both parents revealed maternal carriership of NM_017909.2:c.713A>G, p.Asn238Ser and paternal carriership of the NM_017909.2:c.533C>T, p.Thr178Met. Sanger sequencing of both parents and the two children confirmed the segregations of the variants.

The maternal variant is an A to G transition in exon 5 leading to an Asn238 to Ser missense substitution. This variant is located in protein domain DUF155 of unknown function. The paternal variant shows a C to T transition in exon 3 leading to a Thr178 to Met missense substitution not located in any specific protein domain. Predictive algorithms PolyPhen and SIFT state that both alleles are deleterious and probably damaging, respectively. Both mutations cause a modification of a highly conserved amino acid that might play a role in the structure and/or function of the protein. Allele frequencies in the GnomAD database are as follows: T=0.00002 (6/245972) for the paternal allele and G=0.00019 (46/244478) for the

maternal allele. For both variants the ACMG classification is Pathogenic (II) PS1, PS3, PS4, PM3, PP1-M, PP4, PP3.

Table 1 summarizes their main clinical characteristics and reviews all previous published cases. This retrospective series of cases was approved by the local Institutional Review Board (Comité d'éthique des Hospices Civils de Lyon, session 7 June 2018).

3. Discussion

We report two pediatric cases of a compound heterozygous *RMND1* mutation in two siblings presenting with severe renal hypoplasia but different severity levels of extrarenal comorbidities. Similar to previously published papers, we confirm the prevalence of renal involvement in *RMND1* mutations: Yi Shiau Ng et al. reported a 66% and 38% prevalence of CKD and ESRD, respectively[2]. Summarizing all published cases (Table 1) we report a prevalence of 28 out of 38, 73% of patients with documented (severe) renal disease. All three cases reported by Janer et al. displayed renal abnormalities but were unfortunately not detailed [1].

In most mitochondrial diseases, renal impairment is often observed and has a great influence on the long-term outcomes. To prevent ESRD early in life, or at least to delay the onset of ESRD, it is of utmost importance to monitor renal function and blood pressure in these patients, with information on nephron-protective lifestyle measures early in life.

Renal transplantation has already been reported in four patients [2], with overall positive results on renal function without signs of degradation of their existing neurological impairment. Notably, none of these patients had significant cardiac impairment before transplantation, as described. For our first patient, despite moderate psychomotor delay,

cardiac function was normal and renal transplantation was performed without major complications.

However, besides the medical and technical aspects of renal management of ESRD in these patients suffering from multi-organ failure, there is an ethical dimension to discuss as well. We believe that RRT, which can be considered as a relatively invasive treatment for renal insufficiency, should be considered in these children presenting a mild neurological impairment and no or mild cardiomyopathy. Nevertheless, developmental delay is described in 76% of all the published cases (missing data in eight cases), but the severity was not always reported. Seizures are reported in 36% (missing data for four patients). Moreover, 24% (9/38) of this group of *RMNDI* patients presents severe cardiac comorbidity and the prevalence of vascular comorbidity (arterial hypertension) is even higher (42%).

In case of dialysis initiation during the pediatric age, subsequent renal transplantation should be performed, depending on local and national possibilities. However, in case of severe extrarenal comorbidities, especially in case of severe cardiomyopathy and/or severe encephalopathy, a multidisciplinary discussion should be held to balance the benefits and harms of such invasive management. These decisions should be carefully considered by physicians and adapted to the individual patient's and parents' needs (shared decision making). It should not be performed in children who suffer from multiple comorbidities, especially neurologic and cardiologic impairment.

The second patient we described is an example of the above-stated ethical difficulties that can be encountered. We had to discuss whether it was possible to propose RRT in a context of both severe cardiomyopathy (significantly increasing the risk of major perioperative and intradialytic complications) and severe encephalopathy. After a thorough multidisciplinary discussion, it was considered that cardiac function was too severely impaired and incompatible with dialysis. Indeed, the underlying cardiomyopathy would not

have allowed us to perform hemodialysis, because of hemodynamic changes observed during sessions. The possibility of peritoneal dialysis was also discussed, since it would have been less invasive. However, in the context, a renal transplantation did not appear reasonable. The parents were informed and it was decided to respect the patient's quality of life as much as possible. The decision was even more difficult to make since the medical team and the parents had the example of the older brother, who had normal renal function after renal transplantation. However, despite similar genetic mutations, the clinical severity of the neurological and cardiac impairment was completely different.

4. Conclusion

In summary, we report on a compound heterozygous mutation in the *RMND1* gene in two siblings, leading to severe renal impairment but a different severity level in terms of extrarenal comorbidities. We hereby complete the already existent database of patients and contribute to current knowledge of the wide variety of phenotypes existing. Moreover, we highlight the ethical issues on renal replacement therapy (or other therapies known to be invasive) and the complexity of elaborating a long-term prognosis [6]. This type of case should be handled with specific multidisciplinary care and approached with shared decision making on the part of the caregivers, parents, and patients. Today, everything seems possible but not everything is beneficial.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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Table 1 Summary of all published cases including the two cases described herein in italics (n = 38)

Patient	Ethnicity/Nationality	Onset	FTT	MC	DD	SNHL	Tone	SZ	Renal	Cardiac	Lactate elevation	RMND1 mutation
1 (F)	Italian	At birth	+	+	+	+	C	+	CD, RTA, ESRF, A	HTN	+	c.713A>G p.(Asn238Ser); c.1303C>T
2 (M)	Caucasian	2 Months	-	ns	+	+	C	-	ESRF	HTN, HCM	+	p.(Leu435Phe) c.713A>G p.(Asn238Ser); c.565C>T
3 (F)	Irish	At birth	+	+	+	+	Normal	-	RTA, ESRF	HTN, HCM, PDA, PT	+	p.(Gln189*) c.713A>G p.(Asn238Ser); c.533C>A
4.1 (M)	Caucasian	6 Months	-	-	+	+	C, P	+	CD, ESRF, Tx	HTN	-	p.(Thr178Lys) Homozygous c.713A>G
4.2 (M)	Caucasian	6 Months	+	+	+	+	C, P	+	-	-	-	Homozygous c.713A>G p.(Asn238Ser)
5 (F)	Caucasian, Native American	At birth	+	+	+	+	C,P	+	CD, ESRF, Tx	HTN	+	Homozygous c.713A>G p.(Asn238Ser)
6 (M)	European, Mexican	At birth	+	-	+	+	C	-	CD, RTA, ESRF, Tx	HTN, mild LVH	+	c.713A>G p.(Asn238Ser); c.1317+1G>T, p.?
7.1 (F)	Caucasian	12 months	-	-	+	+	Normal	-	CKD stage 2, A	-	Metabolic acidosis, normal lactate	c.713A>G p.(Asn238Ser); c.1250G>A p.(Arg417Gln)
7.2 (F)	Caucasian	12 Months	-	-	+	+	Normal	-	CKD stage 3, A	-	Metabolic acidosis, normal lactate	c.713A>G p.(Asn238Ser); c.1250G>A p.(Arg417Gln)
8 (F)	Caucasian	At birth	+	+	+	+	Normal	+	RTA, CKD stage 4	HTN	+	c.631G>A p.(Val211Met); c.830+1G>A p.(Met244Glyfs*20)
9 (M)	Pakistani	1 Month	+	-	+	+	C	-	RTA, ESRF, A	HTN, HB	+	Homozygous c.1349G>C p.(*450Serext*31)
10.1 (F)	Bangladeshi	3 Months	+	-	+	+	C	-	RTA, ESRF, A	Pericardial effusion, HB	+	Homozygous c.1349G>C p.(*450Serext*31)
10.2 (F)	Bangladeshi	9 Months	+	-	+	+	C	-	RTA, ESRF, A	HTN, HB (pacemaker)	+	Homozygous c.1349G>C p.(*450Serext*31)
11.1 (F)	Pakistani	8 Months	+	+	+	+	C	-	CD (at autopsy)	HB	+	Homozygous c.1349G>C p.(*450Serext*31)
11.2 (F)	Pakistani	3 Months	+	+	+	+	C	-	RTA, A	-	+	Homozygous c.1349G>C p.(*450Serext*31)
12 (F)	Pakistani	18 Months	+	+	+	+	C	-	CD, RTA, ESRF	DCM	-	Homozygous c.1349G>C p.(*450Serext*31)
13 (F)	Pakistani	6 Months	+	+	+	+	C	-	RTA	Small VSD, HB	+	Homozygous c.1349G>C p.(*450Serext*31)
14 (M)	Pakistani	6 Months	+	-	+	+	C	-	CD, RTA, ESRF	HTN, HB	+	Homozygous c.1349G>C p.(*450Serext*31)

15 (F)	Pakistani	1 Month	+	+	+	+	C	-	CD, ESRF	HB	-	Homozygous c.1349G>C p.(*450Serext*31)
16 (F)	Irish	1 Month	+	+	+	+	P	+	RTA, CKD stage 4	HTN	+	c.713A>G p.(Asn238Ser); c.829_830+2het_delGAGT p.?
17.1 (M)	Sudanese	At birth	ns	+	+	-	C, P	+	-	-	+	Homozygous c.1250G>A p.(Arg417Gln)
17.2 (M)	Sudanese	At birth	ns	ns	ns	-	C, P	+	-	-	+	Homozygous c.1250G>A p.(Arg417Gln)
18.1 (F)	Caucasian	14 Months	+	-	+	+	C	-	Proteinuria, ESRF, Tx	HTN	ns	c.713A>G p.(Asn238Ser); c.1003delG p.(Ala335Leufs*2)
18.2 (F)	Caucasian	At birth	+	-	+	+	C	+	Proteinuria ; ESRF, A, Tx	HTN	ns	c.713A>G p.(Asn238Ser); c.1003delG p.(Ala335Leufs*2)
19 (M)	Caucasian	At birth	+	-	+	+	C	+	RTA, A, CD (autopsy)	HTN, LVH	+	c.613G>T p.(Asp205Cysfs*4); c.713A>G p.(Asn238Ser)
20.1 (F)	ns	2 months	ns	+	ns	ns	C	+	-	ns	+	Homozygous c.1250G>A p.(Arg417Gln)
20.2 (F)	ns	Neonatal period	+	+	ns	ns	C	+	-	ns	+	Homozygous c.1250G>A p.(Arg417Gln)
21.1 (M)	Saudi Arabian	At birth	ns	ns	ns	ns	C	+	-	ns	+	Homozygous c.504+1G>A, p.?
21.2 (M)	Saudi Arabian	At birth	ns	ns	ns	ns	C	ns	-	ns	+	Homozygous c.504+1G>A, p.?
21.3 (F)	Saudi Arabian	At birth	ns	ns	ns	ns	C	ns	-	ns	+	Homozygous c.504+1G>A, p.?
21.4 (M)	Saudi Arabian	At birth	ns	ns	ns	ns	C	ns	-	ns	+	Homozygous c.504+1G>A, p.?
21.5 (F)	Saudi Arabian	Stillborn	ns	ns	ns	ns	ns	ns	ns	ns	ns	Homozygous c.504+1G>A, p.?
22 (F)	Caucasian Portuguese	7 years	+	ns	-	+	Normal	-	Distal RTA	ECG normal		c.713A>G p.(Asn238Ser)
23 (ns)	ns	Neonatal period	ns	ns	+	+	C	-	+Not further specified	ns	+	c.533C>T p.(Thr178Met) and c.713A>G p.(Asn238Ser)
24 (ns)	ns	2 Months	ns	ns	+	+	C	-	+ Not further specified	ns	+	c.533C>T p.(Thr178Met) and c.713A>G p.(Asn238Ser)
25 (ns)	ns	At birth (prenatal period)	ns	ns	+	+	C	+	+ Not further specified	ns	+	c.713A>G p.(Asn238Ser) and c.485del p.(Pro162Glnfs*5)
26.1 (M)	Caucasian French	At birth	+	-	+	+		-	HD, ESRD, dialysis at the age of 13, Tx	HTN	+	c553C>T p.(Thr178Met) and c.713A>T p.(Asn238Ser)
26.2 (F)	Caucasian French	3-6 Months	+	-	+	+		-	HD, ESRD	HTN, Cardiac insufficiency, LVEF of 15%	+	c553C>T p.(Thr178Met) and c.713A>T p.(Asn238Ser)

A, anemia; CD, cystic dysplasia; CKD, chronic kidney disease; DCM, dilated cardiomyopathy; ESRD, end-stage renal disease; F, female; FTT, failure to thrive; GH, growth hormone; HB, heart block; HCM, hypertrophic cardiomyopathy; HD, hypodysplasia; HTN, hypertension; LVEH, left ventricle ejection fraction; LVH, left ventricular hypertrophy; M, male; MC, microcephaly; PDA, patent ductus arteriosus; PT, pulmonary hypertension; RTA, renal tubular acidosis; SNHL, sensorineural hearing loss; SZ, seizures; Tx, renal transplantation; VSD, ventricular septal defect; +, presence; -, absence; ns: not stated/unknown. Note: patients 1-21.5 were previously described by Ng et al. [2]. Patient 22 was previously described by Demain et al. [4]. Patients 23-25 were previously described by Ulrick et al. [3]