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NDUFAF5 variants manifest phenotypically heterogeneously

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Letter to the Editor

With interest we read the article by Simon et al. about 4 patients with complex-I deficiency due to mutations in the *NDUFAF5* gene [1]. The phenotype and the outcome of these 4 patients varied considerably [1]. We have the following comments and concerns.

The main shortcoming of this case series is that no prospective studies for multisystem involvement had been carried out. Multisystem disease in mitochondrial disorders (MIDs) may be subclinical or mild and thus frequently overlooked, why these patients need to be systematically investigated for multiorgan affection. Additionally, no comprehensible explanation for the marked phenotypic variability was provided.

MRI in patient-4 revealed DWI hyperintense serpiginous lesions [1]. To clarify if these lesions represent a cytotoxic or vasogenic edema it would be helpful to know the results of the ADC maps. Hypointensity of the ADC maps would suggest cytotoxic edema and thus ischemia, whereas hyperintense ADC maps would suggest vasogenic edema and thus a stroke-like lesion, which would require treatment with NO-precursors, antiepileptic drugs (AEDs), antioxidants, and steroids [2].

In patient-3 arterial hypertension was attributed to administration of ACTH (Table 1) [1]. However, patient-1 had arterial hypertension in the absence of a plausible trigger. Since arterial hypertension has been

Table 1
Findings in the 4 reported patients.

Patient	1	2	3	4
Ethnicity	Taiwanese	Taiwanese	Caucasian	Ashkenazi
Age	10 m	7 y	4 m	12 m
Sex	Female	Female	Male	Male
Onset	6 m	27 m	1 m	Birth
Onset manifestation	Dysphagia	Strabism	Reflux	Develop. delay
Phenotype	Head drop	Oligohydramnion	Irritability	Torticollis
	Nystagmus	Ptosis	Insomnia	Nystagmus
	Blepharospasm	Vomiting	Seizures	Head bobbing
	Vomiting	Optic atrophy	Truncal hypotonia	Hypotonia
	Hypotonia	Fatigue	Limb spasticity	Dysmorphism
	Weight loss	Muscle Weakness	Cortical blindness	Dysphagia
	SIADH	Headache	Dysphagia	Vomiting
	Hypertension	Tremor		
		Contractures		
		Spasticity		
		Hypertension		
		Seizures		
		Pruritus		
		GI dysmotility		
Hyponatriemia	Yes	Yes	No	No
Lactic acidosis serum	Yes	No	Yes	Yes
Lactic acidosis CSF	nd	No	Yes	Yes
Amino acids serum	nd	Normal	Abnormal	nd
Abnormal UOAs	Yes	Yes	Yes	No

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Table 1 (*continued*)

Patient	1	2	3	4
MRI lesions	Thalamus Midbrain CC dysgeneis	Medulla Upper cervical cord	Thalamus Midbrain	Thalamus DWI
Muscle biopsy	nd	Fat droplets	RRF	nd
Biochemistry	nd	Normal	C-I defect	nd
Gene	NDUFAF5	NDUFAF5	NDUFAF5	NDUFAF5
Mutations	c.155A > C c.836 T > G	p.Met279Arg	c.327G > C	c.327G > C c.749G > T
Treatment	Thiamine Coenzyme-Q10 L-carnitine Propranolol Hydrochlorothiazide	Thiamine Coenzyme-Q Riboflavin L-carnitien Labetalol Propranolol Captopril Gabapentin Lisinopril Enalapril	ACTH Hydralazine Amlodipine Enalapril Vigabatrin	Biotin Pantotheniacid Thiamine L-carintine Fundoplication
Outcome	Death at 25 m	Alive at 19 y	Death at 6 m	Death at 17 m

SIADH: syndrome of inappropriate atidiuretic hormone secretion, CSF: cerebrospinal fluid, UOAs: urine oranic acids, CC: corpus callosum, GI: gastrointestinal, RRF: ragged-red fibers, ACTH: adreno-corticotropic hormone, nd: not done.

repeatedly reported as a primary manifestation of mitochondrial disorders (MIDs) [3], it is conceivable that arterial hypertension in patient-1 as well as patient-3 was a primary phenotypic manifestation of the *NDUFAF5* mutation.

Both Taiwanese patients had severe hyponatremia (Table 1) [1]. We should be informed if this was due to primary or secondary hypoaldosteronism, or due to pituitary insufficiency, occasionally occurring as endocrine manifestations of a MID [4].

Overall, this case study could be more meaningful if clinical variability and MRI-findings in patient-3 would have been more extensively discussed and if all patients would have been systematically investigated for multisystem involvement.

Conflict of interest

There are no conflicts of interest.

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