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LETTER TO THE EDITOR

NAD(P)HX dehydratase (NAXD) deficiency: a novel neurodegenerative disorder exacerbated by febrile illnesses

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Sir,

The article by Van Bergen *et al.* (2019) describes the first patients with biallelic *NAXD* mutations, presenting with fever-induced neurological deterioration and repeated episodes of skin lesions. Vitamin B3 (nicotinamide) was not reported to have been administered in these cases, a therapy speculated to be of use in alleviating deficiency in the nicotinamide nucleotide repair system (Kremer *et al.*, 2016). Here we describe a further case with *NAXD* biallelic variants, both of which are novel, in a Chinese patient with a phenotype in-keeping with that described in Van Bergen *et al.* In this case, high dose vitamin B3 therapy showed beneficial therapeutic effect in resolution of skin lesions, a predominant clinical feature of *NAXD* defect, and in stabilization of neurological symptoms in the absence of harmful side effects.

Catabolism and anabolism happen perpetually throughout the body, processes through which metabolic side-products may be produced. NAD(H) and NADP(H) are major redox equivalents in either catabolic or anabolic reactions (Ying *et al.*, 2008). Both are prone to hydrating at acidic conditions, at elevated temperature, or enzymatically, forming NAD(P)HX. NAD(P)HX can be present as R or S epimers and can further degrade irreversibly to cyclic NAD(P)HX. The accumulation of such side-products inhibits key metabolic reactions. Metabolite repair systems remove or recycle these harmful side-products to prevent toxic effect (Linster *et al.*, 2013; Van Schaftingen *et al.*, 2013). NAXD [NAD(P)HX dehydratase, MIM*615910] together with NAXE [NAD(P)HX epimerase, MIM*608862] make up the nicotinamide nucleotide repair system, a system to clear metabolic side-products ensuring efficient and precise metabolism. NAXE converts R-NAD(P)HX to S-NAD(P)HX, while NAXD converts S-NAD(P)HX back to NAD(P)H (Marbaix *et al.*, 2011) (Supplementary Fig. 1). Aberrant function in the nicotinamide nucleotide repair system can result in disease, with deficiency in both NAXE and NAXD confirmed to be related to fever-induced neurological deterioration. To date, four studies report 17 cases with *NAXE* or *NAXD* defect (Kremer *et al.*, 2016; Spiegel *et al.*, 2016; Van Bergen *et al.*, 2019) (Table 1). Here, we report a patient presenting with fever-induced neurological deterioration and repeating skin lesions, in whom whole exome sequencing (WES)

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Table 1 Clinical features of patients with *NAXD* and *NAXE* mutations

Clinical features	Cases with *NAXD* mutations		Cases with *NAXE* mutations	
	Present study	Van Bergen *et al.*, 2019	Kremer *et al.*, 2016	Spiegel *et al.*, 2016[c]
Gender	Male	2 male, 4 female	4 male, 2 female	2 male, 3 female
Age at onset <3 years	Yes	5/6	6/6	5/5
Age at death <5 years	No	6/6	6/6	4/5
Development retardation before onset	No	2/6	3/6	0/5
Fever prior to deterioration	Yes	6/6	4/6	5/5
Skin lesions	Yes	4/6	4/6	0/5
Other systemic involvement	Repeated vomiting	Pancytopenia 3/6 Repeated vomiting 2/6 Heart failure 1/6	0/6	No
Undulating disease course	Yes	3/6	4/6	2/5
Elevated lactate in CSF or serum	No	2/6	6/6	0/5
Lesions in MRI				
Cortex	No	3/5[a]	1/4[b]	0/5
White matter	No	3/5	1/4	5/5
Basal ganglia	Yes	4/5	1/4	0/5
Brainstem	No	1/5	2/4	0/5
cerebellum	Yes	0/5	4/4	5/5
Spinal cord	No	0/5	4/4	0/5

[a]Only five of the six patients had MRI results.
[b]Only four of the six patients had MRI results.
[c]The five patients were siblings of consanguineous family.

demonstrated two novel compound heterozygous variants in the *NAXD* gene.

At the age of 2 years 10 months this child was first admitted to hospital presenting with a 20-day history of skin lesions and involuntary movements. He is the first child of non-consanguineous parents, born at full term in good condition with a birth weight of 3.1 kg. His global and motor development were normal with the milestones of independent walking and speaking words achieved by 1 year 2 months and 1 year 5 months of age, respectively. Prior to this admission he was able to run and speak complete sentences. He had previously suffered from red papular skin lesions around the eyes and the natal cleft on two occasions between the age of 1 and 2 years, for which a trigger could not be identified. The lesions persisted for 2–3 weeks before resolving spontaneously. Twenty days prior to this admission, following a febrile upper respiratory tract infection, skin lesions reoccurred on the upper eyelids, dorsum of the hands, around the mouth, and at the natal cleft, which subsequently developed into purple patches [Fig. 1A(i–iii)] . Simultaneous presentation with involuntary movements, manifesting as blinking of the eyelids, head shaking, and athetosis were documented. The initial cerebral MRI 5 days following disease onset revealed mild oedema of the cerebellum [Fig. 1B(i–iv)] and an EEG displayed slow waves in bilateral occipital regions. Cell count, glucose, protein and lactate of the CSF were all normal. Normal investigations also included hepatic and renal function, serum electrolytes, blood glucose, lactate and ammonia. Metabolic investigations including amino acids, organic acids and acylcarnitine were negative. Given this presentation, autoimmune encephalitis was initially suspected and treatment with intravenous (i.v.) immunoglobulin and glucocorticoid was commenced. His neurological symptoms continued to progress with disturbance of consciousness, frequent involuntary movements, hypermyotonia, and repeated episodes of non-projectile vomiting. Though neurologically deteriorating, his skin lesions gradually improved. A further cerebral MRI 2 weeks following disease onset revealed symmetrical T_2 intensity changes in the basal ganglia associated with restricted diffusion with oedema in bilateral cerebellar hemispheres [Fig. 1B(v–viii)]. Considering his condition and MRI deterioration, he was transferred to a specialized hospital for further investigation. Spinal MRI was normal. Extensive viral studies and toxicology screening were normal. Neuronal surface antibodies in the serum and CSF and oligoclonal bands were negative. Serum biotin was mildly reduced (154.54 ng/l, normal range 250–800 ng/l). Biotinidase assays were normal (171.09%, normal range >30%). Skin biopsy showed extensive necrosis of the epidermis and detachment from the underlying dermis with a few lymphocytes around the vessels in the upper dermis [Fig. 1A(ix and x)]. At this point, he was suspected of biotin-thiamine responsive basal ganglia disease or mitochondrial disease in combination with drug eruption and gastroenteritis. Given this clinical suspicion a 'mitochondrial antioxidant cocktail' therapy of biotin 10 mg/kg/d, vitamin B1 10 mg/kg/d, vitamin B2 5 mg/kg/d, vitamin C 20 mg/kg/d, vitamin E 10 mg/kg Qod, CoQ10 5 mg/kg/d, idebenone 10mg/kg/d, and carnitine 200 mg/kg/d was commenced. Two months later, the patient's neurological status had recovered to baseline and skin

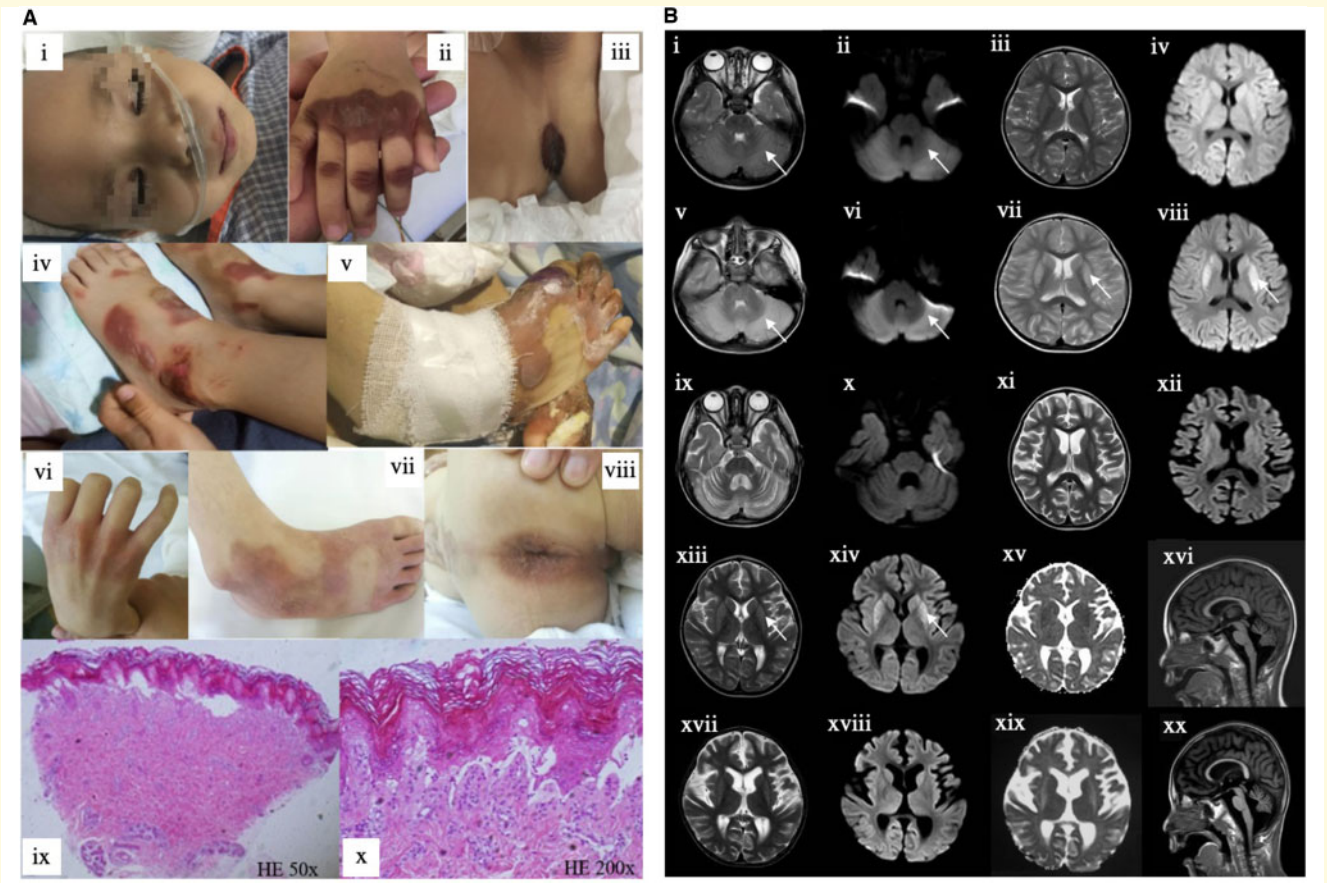

Figure 1 Skin manifestations and neuroimaging findings in a patient with *NAXD* mutations. (**A**) Skin lesions in first episode (**i–iii**), second episode (**iv**) and third episode (**v**). Skin lesions left pigmentation at last follow-up (**vi–viii**). Skin biopsies showed detachment of the epidermis from the underlying dermis with a few lymphocytes around vessels in upper dermis (**ix–x**). (**B**) Cerebral MRI five days after onset axial T_2-weighted image shows high signal (**i**, arrow) and increased diffusion-weighted image (DWI) signal observed in (**ii**) in cerebellum (arrow), and no lesions in basal ganglia (**iii** and **iv**). Repeated MRI 2 weeks later shows high T_2 signal (**v**, arrow) and increased DWI (**vi**, arrow) in cerebellum, and bilateral symmetrical basal ganglia involvement observed on T_2-weighted image (**vii**, arrow) and DWI (**viii**, arrow). Two months after onset MRI showed relief of abnormal intensity in cerebellum with mild atrophy (**ix** and **x**) and in basal ganglia (**xi** and **xii**). One year after onset MRI axial T_2-weighted image shows mild high signal (**xiii**, arrow), increased DWI signal (**xiv**, arrow), decreased apparent diffusion coefficient (ADC) in bilateral symmetrical basal ganglia (**xvii**), and cerebellum atrophy in sagittal T_1-weighted image (**xx**). Two years and 2 months after onset (at last follow-up) demonstrated relief of abnormal signals in bilateral basal ganglia with brain atrophy (**xvii–ix**) and worsening of cerebellum atrophy (**xvi**).

lesions entirely resolved without scarring. He had no involuntary movements and could run, jump, and speak complete sentences. Furthermore, his cerebral MRI demonstrated resolution of the abnormal intensity in basal ganglia and brain atrophy [Fig. 1B(iv–xii)]. At this time, sequencing of a panel of genes associated with inherited metabolic disorders and of the entire mitochondrial genome (mtDNA) did not reveal the molecular cause of his disease.

At 3 years and 10 months of age the patient suffered from a second episode of similar presentation with gradual onset again following febrile illness. He presented with unsteadiness in walking and skin lesions on the upper eyelids, natal cleft, and dorsum of the hands and feet, which later blistered and ruptured particularly on the dorsum of the feet [Fig. 1A(iv)]. He was readmitted to hospital with developmental regression, consisting of loss of the abilities to sit, stand alone, follow an object, swallow, and speak, and with persistent dystonia during wake. Cerebral MRI revealed bilateral cytotoxic oedema of the basal ganglia [Fig. 1B(xiii–xvi)]. In addition to the 'mitochondrial antioxidant cocktail' therapy, trihexyphenidyl, levodopa, and nitrazepam were prescribed to relieve the dystonia. His symptoms showed mild improve after discharge. He could follow an object and eat a semi-liquid diet orally, though his dystonia was still apparent. Complete remission of the skin lesions was documented by 4 years 1 month. At 4 years 5 months the patient stopped the 'mitochondrial antioxidant cocktail' therapy because of lack of health insurance to support his prescription. Table 1 summarizes the clinical characteristics of this patient and six further published cases with *NAXD* defect (Van Bergen *et al.*, 2019).

After obtaining informed consent from the parents, WES of the patient and parental samples were analysed by a trio-analysis resulting in the identification of compound heterozygous variants, c.101_102delTA (p.Thr35Phefs*63) and c.318C>G (p.Ile106Met), in the *NAXD* gene (NM_001242882.1), and confirmed by Sanger sequencing (Supplementary Fig. 2). The p.Thr35Phefs*63 variant is unreported in gnomAD. The p.Ile106Met variant is reported with a MAF (minor allele frequency) of 7.97×10^{-6} (2/250 798 alleles) in gnomAD with no homozygotes and is not detected in 508 alleles from Chinese patients. Although the protein function resulting from these variants is not investigated here, convincing evidence of their pathogenicity, in addition to the patient's clinical presentation being in-keeping with that previously reported in NAXD, can be found. The frameshift mutation (p.Thr35Phefs*63) is predicted to cause protein truncation leading to loss of function. The missense mutation (p.Ile106Met) is predicted to be probably damaging by PolyPhen-2 and deleterious by PROVEAN. According to sequence alignment the Ile106 residue is highly conserved across species, indicating evolutionary importance (Supplementary Fig. 2). Supplementary Table 1 summarizes all reported pathogenic NAXD variants to date.

So far, we have no effective treatment for disorders of the nicotinamide nucleotide repair system. As the function of this system is in converting NAD(P)HX to NAD(P)H abnormality may result in lack of NAD(P)H, the active form of nicotinic acid (Ying *et al.*, 2008). A chronic lack of nicotinic acid (vitamin B3) is known to cause pellagra, a disease presenting with skin lesions and ataxia, as similarly reported in this patient (Hegyi *et al.*, 2004). For these reasons, vitamin B3 supplementation was considered to be of potential benefit to this patient and high dose vitamin B3 (500 mg/d) therapy was commenced upon relapse of the skin lesions with greater severity and extensity at 4 years and 6 months of age [Fig. 1A(v)]. The lesions improved significantly with treatment [Fig. 1A(vi–ix)] and neurological symptoms stabilized. At his last follow-up at 5 years of age there had been no further clinical deterioration or relapse. His MRI at this time revealed relief of old lesions with brain atrophy [Fig. 1B(xvii–xx)].

Although at this time it is too early to determine whether these are truly treatable disorders, we conclude that vitamin B3 holds promise in alleviating skin lesions and stabilizing clinical course without side effect in NAXD defect. As the episodic symptoms characteristically follow fever, early fever control also presents a simple measure for relapse prevention. Moreover, reported here is the longest surviving patient with NAXD defect, leading to speculation that 'mitochondria antioxidant cocktail' therapy may be of benefit in disorders of the nicotinamide nucleotide repair system.

Data availability

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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Competing interests

The authors report no competing interests.

Supplementary material

Supplementary material is available at *Brain* online.

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