High-Dose Nicotinamide Rescues from 'Early-Onset, Progressive Encephalopathy with Brain Edema and/or Leukoencephalopathy-1 (PEBEL-1)': All hope is not lost!

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Introduction

- Early-onset progressive encephalopathy with brain edema and/or leukoencephalopathy (PEBEL) is an autosomal recessive condition precipitated by febrile illness leading to rapidly progressive neurologic deterioration. It occurs due to mutation in NAXE gene which encodes for NAD(P)HX epimerase, and is crucial for nicotinamide nucleotide repair system in humans.
- PEBEL has been described as a lethal neuro-metabolic disorder with a fluctuating course. 17 cases have been reported in the literature with only 3 survivors. Out of which, 2 are with significant morbidity and only 1 child has minimal deficits. Regarding the therapeutic approach, Vitamin B3 has been mentioned to have shown positive response in the previous studies.
- We present two cases where high dose nicotinamide has not only ensured survival, but prevented crises as well.

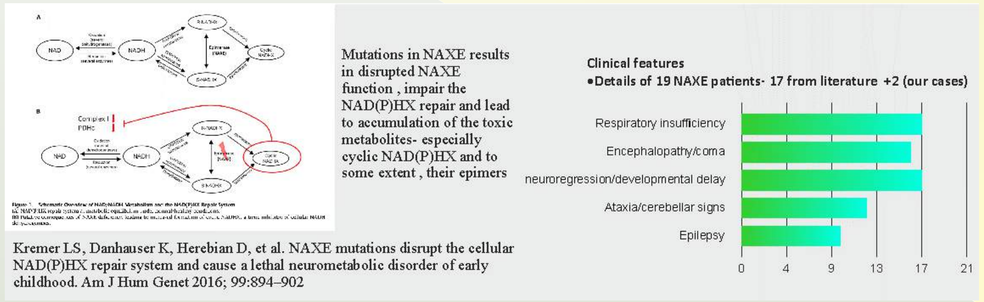
Case-1

- 16 months-old girl with mild developmental delay, presented with acute neuroregression, seizures and rapidly progressive encephalopathy, following febrile illness, necessitating mechanical ventilation. She had GCS 3/15, bilateral external ophthalmoplegia, absent breathing, autonomic instability and bilateral pyramidal dysfunction. Her MRI brain and metabolic work-up were normal. There were two sibling deaths in infancy, with developmental delay, acute encephalopathy, hypoventilation and neuroregression. The index child's whole exome sequencing (WES) revealed homozygous pathogenic NAXE mutation. Following Nicotinamide supplementation (200 mg/day), she showed remarkable improvement
- At the last follow up, 4yr 2months, she is walking briskly, running, is able to eat on her own, obeys commands with gestures and socilaizes with peers. She is under hearing rehabilitation. She has focal seizures which are controlled with oxcarbazepine (20mg/kg/day) and clobazam (10mg/day)

Case-2

- A 14 months-old girl presented with acute-onset sensorineural hearing loss and walking difficulty following febrile illness. On examination, she had ataxia, and BERA showed profound hearing loss. Rest of the motor and sensory examination was normal. Her MRI and metabolic work-up were unremarkable.
- There was history of an elder female sibling , who suffered neuroregression and acute-onset esotropia and died at 27 months age, with rapidly progressive encephalopathy and respiratory failure. WES of that child and the index child revealed homozygous pathogenic mutation in NAXE gene.
- After starting Nicotinamide (250 mg/day), her motor functions improved dramatically, but SNHL persisted.
- At the last follow up, she was 18 months, she could walk and run, understood gestures and obeyed commands, though she had failure to thrive and SNHL.

Discussion



Kremer LS, Danhauser K, Herebian D, et al. NAXE mutations disrupt the cellular NAD(P)HX repair system and cause a lethal neurometabolic disorder of early childhood. Am J Hum Genet 2016; 99:894–902

- Mutations in NAXE results in disrupted NAXE function , impair the NAD(P)HX repair and lead to accumulation of the toxic metabolites- especially cyclic NAD(P)HX and to some extent , their epimers
- Cerebrospinal fluid may show elevated lactate.
- The MRI findings can be variable .It can range from no significant abnormality to diffuse cerebral edema or cortical atrophy, white matter signal changes or gross cortical .In one of our patient , there was diffuse cortical atrophy. Myelopathy in spine MRI has been reported earlier and our case also had some signal changes in cervico-thoracic spine
- Diagnosis is through whole exome sequencing
- As the underlying system affected in this disease is NAD/NADP+ metabolism, hence nicotinamide -the precursor for these co-factors can be tried as a therapeutic option. The lack of proper NAD+ levels caused by insufficient epimerization of NAD(P)HX due to the hypomorphic NAXE mutations may be improved with vitamin B3 treatment. NAD+ pools can be restored by supplementation of vitamin B3, which may help ameliorate patients' cell metabolism.
- With this hypothesis, it has been tried in patients in low dose (30-40mg/day) along with Co-enzyme Q (150mg/d) along with other supportive and symptomatic management. It led to significant reversal of spasticity and fine motor and cognitive improvement in a patient. It was used only in acute phase in another patient and the patient recovered well.
- We tried a higher dose of nicotinamide (200- 300mg/day) in our cases and the results are promising.

Conclusion

- PEBEL-1 due to NAXE mutations is rare and often fatal condition. Early diagnosis and timely initiation of high dose nicotinamide can facilitate good recovery, and prevents neurological crises
- High-dose Nicotinamide has helped in recovery from acute crisis, survival and improvement in neurological status in this fatal genetic disorder. There are very few survivors with this condition. Its important to make physicians aware of this potentially treatable disorder

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