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RESEARCH ARTICLE

CASE OF NAXD DEFICIENCY PRESENTING WITH DEVELOPMENTAL REGRESSION AND PROGRESSIVE ENCEPHALOPATHY

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Abstract

Introduction: Developmental regression in children can indicate underlying neurodegenerative or metabolic diseases, often posing diagnostic and therapeutic challenges. Defects in NAD(P)HX dehydratase (NAXD), an enzyme crucial for maintaining cellular NAD(P)H levels, are implicated in progressive encephalopathy. This case report highlights NAXD deficiency as a rare but critical cause of developmental regression, with a focus on genetic findings and clinical presentation.

Case Presentation: A 9-month-old infant with a history of normal development until 7 months of age presented with rapid developmental regression, including loss of motor skills, social engagement, and speech. Clinical examination revealed hypotonia, hypertonia, exaggerated reflexes, hepatomegaly, and pancytopenia. Genetic testing identified a homozygous mutation in the NAXD gene, confirming the diagnosis. MRI showed brain atrophy and restricted diffusion in the basal ganglia, while MRS indicated metabolic abnormalities. Despite supportive therapy, the child developed seizures, respiratory failure, and multiorgan dysfunction, eventually leading to death.

Discussion: NAXD deficiency leads to toxic accumulation of NAD(P)HX metabolites, impairing mitochondrial function and causing progressive neurological decline. Our case presents atypical features, including the absence of fever-triggered neurological deterioration, which suggests subtle or unnoticed febrile episodes may contribute to symptom exacerbation. The use of whole-exome sequencing (WES) was crucial for diagnosis, aligning with other reports linking NAXD mutations to early-onset encephalopathy and seizures.

Conclusion and Future Directions: This case underscores the importance of early genetic testing in diagnosing rare metabolic disorders like NAXD deficiency. Future research should focus on therapeutic strategies to restore NAD(P)HX balance, including mitochondrial-targeted therapies, and the identification of biomarkers for disease progression. Further studies are needed to optimize clinical management and improve outcomes in affected individuals.

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Introduction:-

Developmental regression in children is a serious clinical sign that often points to the onset of neurodegenerative or metabolic diseases(1). This condition, characterized by the gradual or sudden loss of previously acquired developmental abilities, is a critical indicator of underlying neurological dysfunction(2). The identification and management of these disorders pose significant challenges, as pinpointing the exact cause is often difficult and treatment options are typically limited. Among the numerous conditions that can lead to developmental regression, disturbances in cellular energy metabolism have gained considerable attention due to their profound impact on brain function. One such disorder involves defects in NAD(P)HX dehydratase (NAXD), an enzyme essential for maintaining cellular NAD(P)H levels, which are crucial for normal brain activity(3, 4).

Nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP) are indispensable cofactors involved in a wide range of cellular processes, particularly in energy production and antioxidant defenses(5). NAD is primarily engaged in catabolic reactions, including mitochondrial oxidative phosphorylation, while NADP, along with its reduced form NAD(P)H, supports anabolic reactions and helps protect cells from oxidative stress(6, 7). These cofactors are prone to hydration, resulting in the formation of damaged metabolites, NADHX and NAD(P)HX, which exist as R or S epimers. Under stress conditions such as acidic pH or elevated temperatures, these metabolites can irreversibly cyclize into NAD(P)HX, which inhibits several dehydrogenases and generates toxic byproducts. The accumulation of these abnormal metabolites can be detrimental to cellular function, particularly in the brain, which has high metabolic demands(8, 9).

To mitigate the toxicity of NAD(P)HX, cells have developed a specialized repair system, consisting of two key enzymes: NAD(P)HX epimerase (NAXE) and NAD(P)HX dehydratase (NAXD)(10). NAXE converts the R epimer of NAD(P)HX to the S form, while NAXD processes the S epimer to regenerate NAD(P)H in an ATP-dependent manner. These enzymes are ubiquitously expressed and play a crucial role in maintaining cellular function, especially in energy-intensive tissues like the brain(11). Disruption of this repair system, due to mutations in the NAXE or NAXD genes, leads to the accumulation of toxic metabolites, resulting in severe neurological damage. The brain, due to its high energy requirements, is particularly susceptible to such disruptions, which can cause developmental regression, ataxia, seizures, and other neurological symptoms(12, 13).

Deficiencies in NAXD and NAXE are linked to a range of neurological disorders, often exacerbated by metabolic stress such as fever. These disorders, typically classified as early-onset progressive encephalopathy with brain edema and/or leukoencephalopathy (PEBEL), are marked by rapid and severe neurological decline(14). Affected individuals often experience psychomotor regression, ataxia, hypotonia, seizures, and respiratory failure, with some cases leading to premature death. While mutations in the NAXE gene have been the most commonly identified cause of these conditions, recent studies suggest that NAXD mutations can also result in similar clinical presentations. The mechanisms behind these disorders involve the inability of cells to repair NAD(P)HX metabolites, leading to toxic accumulation and subsequent neuronal dysfunction(11, 15).

This case study aims to present a novel instance of developmental regression associated with a deficiency in NAD(P)HX repair enzymes. We report an infant who exhibited acute neurological decline, including massive brain ischemia, brain edema, and refractory fungal septic shock, accompanied by multiorgan dysfunction. Whole-exome sequencing revealed a homozygous, autosomal recessive mutation in the NAXD gene, providing a genetic diagnosis that links NAXD deficiency to the observed clinical symptoms. This case highlights the importance of considering NAD(P)HX metabolism as a potential underlying cause of developmental regression, especially in cases where fever or metabolic stress triggers rapid neurological deterioration. The mechanism underlying developmental regression in NAXD deficiency is thought to involve the accumulation of toxic NAD(P)HX metabolites, which disrupt vital metabolic functions necessary for normal neuronal activity. The brain's high energy demands make it particularly vulnerable to any dysfunction in NAD(P)H regeneration, leading to rapid neuronal impairment(16).

The clinical picture in NAXD deficiency typically includes rapid neurological deterioration triggered by fever or other metabolic stresses, a feature shared with other disorders affecting NAD(P)HX metabolism, such as PEBEL(12). Despite the rarity of NAXD deficiency, the clinical spectrum appears to overlap with that of other neurodegenerative conditions, making it crucial to consider NAD(P)HX metabolism when evaluating cases of unexplained developmental regression(17). The discovery of a homozygous mutation in the NAXD gene in our

patient adds to the limited body of literature on this condition and further emphasizes the importance of genetic testing in diagnosing rare neurometabolic disorders(4, 18).

By documenting this case, we aim to expand the clinical understanding of NAXD deficiency and its association with severe neurological outcomes, contributing to the growing body of literature on this rare but critical metabolic disorder. The findings underscore the potential role of genetic testing, particularly WES, in diagnosing rare neurometabolic conditions that present with developmental regression, offering insights into personalized treatment strategies and future avenues for research.

Case presentation

At the age of 9 months, the child was first admitted to the hospital for evaluation of developmental regression. He is the first child of consanguineous parents, born at full term without any pre- or postnatal complications. Delivered via spontaneous vaginal delivery with no NICU admission, his development appeared normal until the age of seven months. His parents noticed a loss of previously achieved developmental milestones, including the ability to sit unsupported, smile, and interact with his surroundings.

Upon admission, the child appeared unwell, irritable, pale, and without jaundice or cyanosis. Physical examination revealed axial hypotonia and hypertonia in the limbs, with exaggerated deep tendon reflexes and extensor plantar responses. There was no respiratory distress; bilateral lung entry was good, and no added sounds were present. Cardiovascular examination showed normal heart sounds without murmurs. Abdominal examination revealed hepatomegaly with a liver span of 9 cm, while neurocutaneous stigmata were absent.

Initial laboratory investigations showed normal CBC, which later developed pancytopenia. Iron profile was normal, and metabolic markers such as lactate and ammonia were elevated (4.2 → 1.4 → 4.7 and 146 → 66 → 77 → 68, respectively). G6PD was found to be 1.7, and Protein S and C were within normal limits. Genetic and biochemical analyses, including Tandem Mass Spectrometry (Tandemx MS) and urine GCMS, were normal. Whole Exome Sequencing (WES) identified a homozygous variant in the NAXD gene associated with AR early-onset progressive encephalopathy with brain edema and/or leukoencephalopathy type II. This variant is a common G6PD deficiency variant classified as Class III, leading to moderate-to-mild deficiency according to the World Health Organization's classification.

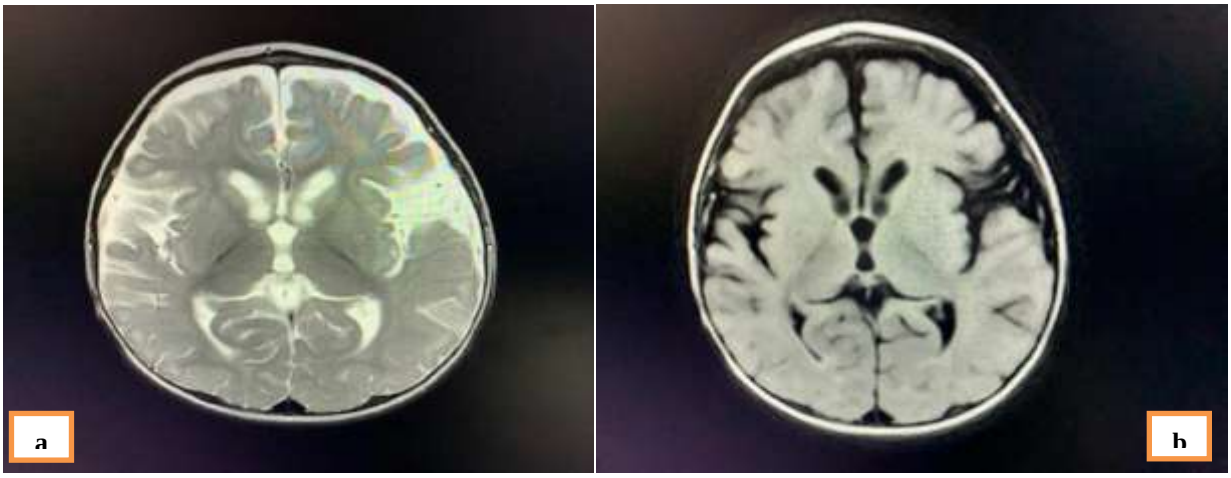

Figure 1 (a,b):- Brain Imaging and Spectroscopy Analysis.

MRI of the brain showed dilated cerebral ventricles, prominent cortical sulci, sylvian fissures, and extra axial CSF spaces, with restricted diffusion to the basal ganglia. Magnetic Resonance Spectroscopy (MRS) revealed a peak of choline and lactate, indicating a neurometabolic disorder.

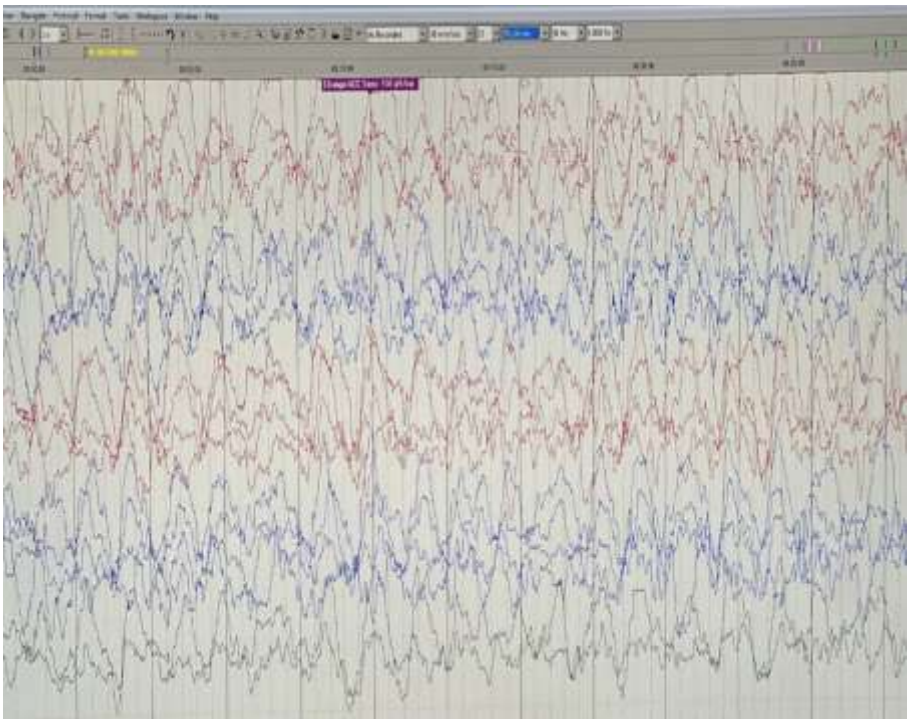

Figure 2:- EEG performed initially showed hypsarrhythmia.

The child was started on a treatment regimen including vigabatrin, thiamine, pyridoxine, riboflavin, biotin, carnitine, and co-enzyme Q. On the second day, he became lethargic, with a deteriorating level of consciousness. A full septic screen was conducted, which was normal, and antibiotics were initiated. After five days, the child was transferred to the PICU due to further deterioration in consciousness (GCS 10/15) and the development of encephalopathy. Despite remaining on room air, he began experiencing tonic seizures in the upper and lower limbs and was started on anti-epileptic drugs. He required mechanical ventilation support and spent approximately three weeks in the PICU. During this period, he was connected to high-frequency oscillatory ventilation with high settings. Unfortunately, he developed refractory fungal septic shock with multiorgan dysfunction and disseminated intravascular coagulation (DIC). Despite aggressive management, he suffered two cardiac arrests and did not respond to resuscitative efforts.

Discussion:-

In this case report, we present a 9-month-old infant who demonstrated a concerning decline in previously acquired developmental milestones, including loss of motor skills, social engagement, and speech. Within a span of one month, the child lost the ability to sit unsupported, exhibited diminished social interaction, and ceased to babble or utter early words such as "Mama" and "Papa." This rapid regression raised significant concern for a neurodegenerative disorder, prompting a comprehensive diagnostic workup. Through whole-exome sequencing (WES) and whole-genome sequencing (WGS), we identified a homozygous mutation in the NAXD gene, confirming a diagnosis of NAXD deficiency. This rare genetic condition disrupts NAD(P)HX metabolism, leading to mitochondrial dysfunction and progressive neurological decline, which is consistent with the clinical presentation observed in our patient(19).

The NAXD gene encodes nicotinamide adenine dinucleotide (NAD) and NAD phosphate (NADP) metabolism-related enzymes that are essential for mitochondrial function, including oxidative phosphorylation and cellular antioxidant defenses(20). NAXD plays a critical role in the repair of NAD(P)HX, a damaged form of NAD(P)H. Mutations in the NAXD gene impair the function of NAD(P)HX dehydratase, leading to the accumulation of toxic NAD(P)HX derivatives, which disrupt cellular energy metabolism, particularly in high-energy tissues such as the brain. This dysfunction is associated with progressive encephalopathy, as evidenced by the severe neurological manifestations in our patient(21, 22).

Our case aligns with previous reports of NAXD deficiency, characterized by developmental regression, psychomotor decline, seizures, hypotonia, and seizures(23, 24). Interestingly, our patient's decline did not follow the typical course observed in many NAXD deficiency cases, in which symptoms are often triggered or exacerbated by fever. Fever-induced neurological deterioration is a common feature reported in the literature, with several studies highlighting the exacerbation of symptoms under such conditions(21, 25). However, in our case, there was no documented fever at the time of symptom onset, which is an atypical presentation of this disorder. This observation suggests that subtle or unnoticed febrile episodes, which may have been overlooked by the parents, could trigger or accelerate the disease process. The absence of fever does not exclude the diagnosis of NAXD deficiency, as the accumulation of toxic NAD(P)HX metabolites could still impair mitochondrial function and lead to progressive neurodegeneration even without an overt fever(26).

The diagnosis of NAXD deficiency in our patient was made using WES and WGS, both of which have become indispensable tools in identifying rare and genetically heterogeneous disorders, particularly those with evolving or atypical clinical manifestations(27). These technologies have enabled the discovery of mutations in the NAXD gene, underscoring their importance in the diagnosis of rare metabolic disorders. Previous studies, including Van Bergen et al. (2019), emphasized the utility of WES and WGS in identifying pathogenic mutations in patients with neurodegenerative disorders, facilitating timely diagnosis and improving the understanding of the disease's genetic basis(3). The identification of the NAXD gene mutation in our case adds to the growing body of evidence linking NAXD dysfunction to early-onset progressive encephalopathy and highlights the role of genetic testing in diagnosing rare metabolic conditions(10, 28).

Neurological regression and subsequent seizures are hallmark features of NAXD deficiency, and these findings were also present in our patient. The patient exhibited a rapid decline in neurodevelopmental milestones and developed tonic seizures, which are consistent with reports from other case studies (29, 30). The EEG findings, which showed hypsarrhythmia, further supported the diagnosis of a neurodegenerative condition with refractory seizures. Hypsarrhythmia is a chaotic, disorganized pattern of electrical activity that is often observed in children with severe neurological conditions such as infantile spasms(31). Our patient's seizures, which were difficult to control despite medical interventions, reflect the refractory nature of seizures in NAXD deficiency, a feature that has been documented in prior reports(32).

Brain imaging, particularly MRI, plays an essential role in evaluating the extent of neurological damage in disorders like NAXD deficiency(33). While our patient's initial MRI was unremarkable, subsequent imaging revealed cerebral atrophy and a thin corpus callosum, consistent with findings reported in other cases of NAXD deficiency. In contrast to other studies, our patient did not exhibit the typical basal ganglia or white matter changes frequently seen in NAXD deficiency. However, the development of symmetrical lesions in the basal ganglia in later MRI scans suggests the neurodegenerative nature of the disease(29, 34). Additionally, MRS findings showing elevated lactate and choline peaks further support the diagnosis of a neurometabolic disorder, highlighting the role of mitochondrial dysfunction in the pathophysiology of NAXD deficiency(35). These neuroimaging findings are consistent with reports by Zhou et al. (2020), who also documented cerebral atrophy and abnormal metabolic patterns on MRS in patients with NAXD mutations(10).

The management of NAXD deficiency remains largely supportive, with no definitive cure available at present. Given the potential mitochondrial dysfunction, our patient was started on a mitochondrial cocktail, which included thiamine, pyridoxine, riboflavin, biotin, carnitine, and coenzyme Q, along with other supportive therapies(36). While the response to this therapy in our patient was not definitive, it aligns with the approach used by Spiegel et al. (2016), who reported partial improvement in neurological function and skin lesions with mitochondrial cocktail therapy(37, 38). This suggests that mitochondrial supplementation may provide some benefit, although further studies are needed to evaluate its true efficacy in NAXD deficiency. Despite aggressive management, our patient's condition deteriorated, leading to refractory fungal septic shock and multiorgan failure. This is consistent with the reported outcomes of other patients with NAXD deficiency, many of whom succumb to progressive encephalopathy, respiratory failure, and sepsis(26, 39).

This case highlights the phenotypic variability observed in NAXD deficiency and underscores the importance of early diagnosis and intervention. The absence of fever at the onset of neurological decline in our patient may suggest that NAXD deficiency can present with subtler symptoms or that febrile episodes may go unnoticed. Additionally,

the use of advanced genetic testing, including WES and WGS, has proven invaluable in diagnosing rare and genetically heterogeneous disorders like NAXD deficiency, particularly in the absence of clear clinical triggers(40).

Strengths and Future Directions

This case contributes significantly to the growing understanding of NAXD deficiency, particularly regarding its phenotypic variability and the role of advanced genomic techniques in diagnosis. The use of WES and WGS has proven instrumental in confirming the diagnosis of NAXD deficiency in this patient, and this approach should be considered in other cases of unexplained neurodegenerative conditions, especially those with developmental regression. The findings in this case, including the atypical presentation without fever and the progression to multiorgan failure, suggest that further research is needed to explore the full spectrum of NAXD deficiency. Future studies should focus on developing therapeutic strategies to restore NAD(P)HX balance, potentially involving mitochondrial-targeted therapies and clinical trials to assess the efficacy of these approaches. The identification of biomarkers that can predict disease progression and response to therapy will also be crucial in managing NAXD deficiency and improving outcomes for affected individuals.

Conclusion:-

In conclusion, this case highlights the critical role of NAXD deficiency in the early onset of progressive encephalopathy and developmental regression. Despite the atypical absence of a fever-triggered onset in our patient, the rapid neurological decline, seizures, and neuroimaging findings point to a mitochondrial dysfunction driven by the accumulation of toxic NAD(P)HX metabolites. The confirmation of this rare disorder through whole-exome sequencing underscores the importance of advanced genetic testing in diagnosing rare neurometabolic conditions, particularly those presenting with developmental regression. While there is currently no definitive cure for NAXD deficiency, the use of mitochondrial cocktail therapy represents a potential, albeit not fully established, avenue for symptom management. Moving forward, further research is essential to elucidate the pathophysiological mechanisms of NAXD deficiency and to explore targeted therapeutic strategies, including mitochondrial support and the identification of biomarkers for disease progression. This case serves as a valuable contribution to understanding the clinical variability of NAXD deficiency and the need for early diagnosis and intervention in rare neurodegenerative diseases.

Statement of Ethics

Ethical approval was not required for this study in accordance with local/national guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to disclose.

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Author Contributions.

All authors contributed equally.

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