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Review Article

Tracing deficiency to disorders: vitamin B12 and the neurological manifestations of infantile seizures and west syndrome

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ABSTRACT

A silent maestro conducts the developing brain's symphony – Vitamin B12. When this vital nutrient goes missing, the music can convulse, leading to infantile seizures. This review delves into the fascinating link between B12 deficiency and the enigmatic West syndrome, a specific seizure disorder in infants. We dissect the intricate mechanisms by which B12 deficiency disrupts these vital pathways, potentially orchestrating this devastating neurological manifestation. One crucial impact area is myelination, the process of insulating nerve fibers with a fatty sheath for efficient signal transmission. Without sufficient B12, this insulation falters, disrupting communication between neurons. This disruption may manifest in the characteristic seizures observed in West syndrome. Furthermore, B12 is essential for producing neurotransmitters, the chemical messengers that shuttle information between brain cells. A deficiency can leads to imbalances in these messengers, potentially triggering abnormal electrical activity and causing seizures. By meticulously analyzing the reported association between B12 deficiency and the well-defined clinical presentation of West syndrome, this article underscores the crucial role of considering this vitamin deficiency in the complex detective work of diagnosing infantile seizures. Early identification and intervention, administered with the precision of a perfectly timed crescendo, can be the key to restoring the harmonious melody of a healthy brain, ensuring proper development and a brighter future for these vulnerable infants.

Keywords: Hypsarrhythmia, Infantile spasms, Neurodevelopmental delays, Vitamin B12 deficiency, West syndrome

INTRODUCTION

Unveiling the potential link between early vitamin B12 deficiency and infantile seizures

Vitamin B12 deficiency, a recognized cause of neurological decline in newborns, can disrupt the developing nervous system, possibly affecting myelin formation and contributing to conditions like infantile seizures and West syndrome.[1] This association, while uncommon, emphasizes the importance of early detection and intervention for best outcomes.

Pioneering research paves the way

In a groundbreaking 1962 study, Jadhav et al. illuminated the neurological consequences of B12 deficiency in infants. Their study, conducted in India, described a constellation of concerning symptoms–apathy, developmental regression, involuntary movements, and altered skin pigmentation – that painted a clear picture of this frequently overlooked condition. This landmark research laid the foundation for further exploration into the intricate relationship between B12 deficiency and the developing brain.[1]

Demystifying west syndrome: a neurological enigma with multiple movements

West syndrome (WS) or infantile spasms, presents a complex neurological puzzle. This epileptic encephalopathy is like a multifaceted condition with a distinctive electroencephalogram (EEG) pattern.

This pattern reveals developmental regression, myoclonic jerks (brief, involuntary muscle twitches) and hypsarrhythmia, a sign of abnormal brain activity that disrupts an average growth and development.

The cause of WS has been a subject of ongoing debate, traditionally categorized as either having a clear cause (symptomatic) or arising from unknown origins (cryptogenic).[2]

However, recent advancements have unveiled a more comprehensive range of potential contributors, including structural brain abnormalities, complications around birth (perinatal insults), inborn metabolic errors (genetic disorders affecting metabolism), and a genetic predisposition for this complex condition.[2,3]

Infantile seizures and the B12 deficiency connection: a story still evolving

The realm of infantile seizures is a kaleidoscope of clinical presentations, each with its own underlying cause, that may have an impact on various neurological outcomes. Notably, vitamin B12 deficiency has emerged as a potential player in this complex scenario, particularly affecting young toddlers.

While uncontrolled movements and convulsions are not always indicative of B12 deficiency, some studies have documented their presence in infants with the condition.

Unraveling the specific link: controversy and the need for further research

The specific association between B12 deficiency and infantile seizures remains under investigation. While Benbir et al, (2007) reported a lack of seizures in their study focusing on neurological manifestations in young children with B12 deficiency, others have observed a more definitive association between the two.[4]

This review aims to synthesize these findings and explore the potential mechanisms by which B12 deficiency might influence infantile seizures and postnatal West syndrome.

The maternal-infant connection: a potential cascade of vitamin B12 deficiency

Much of the data on vitamin B12 deficiency in infants comes from case studies, where the deficiency invariably originated from a mother's vitamin depletion. Two primary factors contribute to maternal vitamin B12 insufficiency.

Dietary intake

Vitamin B12 is exclusively found in animal products like milk, eggs, fish and meat. A low intake of animal-based foods, particularly among strict vegetarians and lactic vegetarians, can lead to nutritional deficits and pose a severe concern for B12 deficiency in their children.

Vitamin B12 deficiency during lactation

A newborn born to a mother with vitamin B12 deficiency stores roughly 25 mg of vitamin B12 at birth and uses 0.1–0.4 mg daily for tissue synthesis.

If a mother does not get enough vitamin B12 during pregnancy, her baby's endogenous stores of the vitamin may be significantly lower at birth.

Exploring the link: mechanisms and evidence

This review delves into the existing body of research on vitamin B12 deficiency in early life. We will evaluate relevant case studies and synthesize findings on the mechanisms influencing its effects on neurodevelopment, particularly concerning vitamin B12 deficiency-related infantile seizures and postnatal West syndrome.

Table 1: Case studies on vitamin B12 deficiency and infantile spasms/west syndrome.

Case study	Age	Presenting seizure type	B12 deficiency	Key finding	Outcome
Chong et al	Seven months	West Syndrome	Yes (Mother and Child)	Autoimmune B12 deficiency in mother	No developmental improvement despite seizure control
Uzunhan et al	Not specified	Seizures	Yes	Cobalamin-related remethylation disorder	West syndrome upon discontinuing B12 treatment
UğurIşık et al	3.5 months	Infantile spasms, Partial seizures	Yes (Mother and Child)	No megaloblasticanemia	Complex neurological profile
Azad et al	8.66 months (ITS), 15 months (WS)	Infantile tremor syndrome (ITS) progressing to	Yes	Vitamin B12 insufficiency linked to eventual WS	Initial improvement, eventual WS despite B12 treatment

Continued.

Case study	Age	Presenting seizure type	B12 deficiency	Key finding	Outcome
		West Syndrome (WS)			
Erol et al	Ten months	West Syndrome	Yes	Exclusively breastfed mother with low B12 intake	Early diagnosis and treatment are crucial for a successful outcome
Irevall et al	Infants	Seizures	Yes	Seizures a significant symptom of B12 deficiency	Early diagnosis and treatment are crucial for normal development
Kirik et al	Eight months	Infantile spasms, Generalized tonic-clonic seizures	Yes	High homocysteine levels	Seizures a significant sign of B12 deficiency

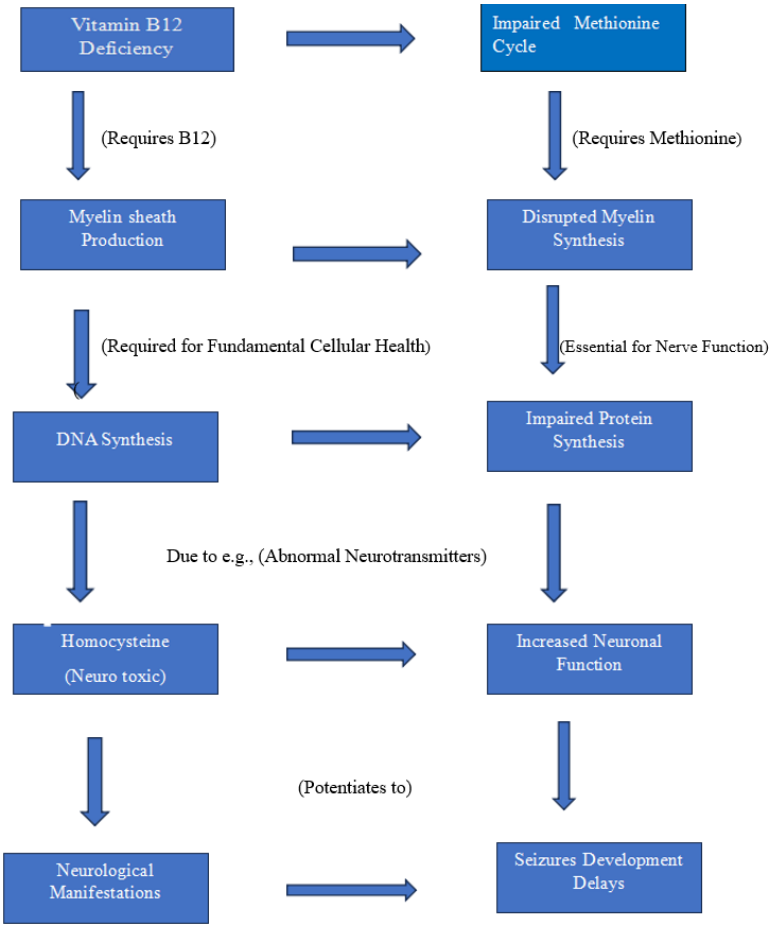

Figure 1: Vitamin B12 and its impact neurological function.

DISCUSSION

Infantile spasms and west syndrome: a historical journey

The history of infantile spasms (IS) and west syndrome (WS) is a fascinating tale of dedicated physicians, pioneering observations, and ongoing research. There are three main stages to this journey that can be distinguished.

A spark in the darkness: the west report (1841)

In 1841, the medical community was introduced to IS and WS through a pivotal case report published in "The Lancet" by Dr. William James West, this report documented the experiences of Dr. West's son, James Edwin, who exhibited seizures at the young age of four months.[14] These initial observations, later termed "Salaam tics," began our understanding of this complex condition. Dr. West, along with his colleague Dr. Langdon-Down,

who later cared for James, documented additional characteristics beyond the seizures. These characteristics included repetitive behaviour, limited language development, and a fascination with music and bright colours, all of which bear similarities to symptoms observed in autism spectrum disorders.

Infantile spasms and west syndrome: navigating the early developmental landscape

Understanding prevalence and demographics

Infantile spasms (IS) and West syndrome (WS) pose a significant challenge within the intricate dance of a child's early neurological development. While the estimated prevalence of IS approximately 0.249 per 1,000 live births, with a prevalence of 1 in 10,000 children by age 10, recent population-based and case-series studies indicate a reassuring stability in the number of affected children.[18,19] This condition manifests in both genders, with males having a slightly higher incidence.

Clinical presentation: The Hallmarks of IS and WS

Clinically, IS presents with brief, synchronized movements of the head, trunk, or limbs. These spasms, lasting about a second, can be flexor, extensor, or a combination of both. The most subtle manifestation is often a simple head nod. West syndrome typically presents between 4 months and two years of age, although it can occur in older children as well. Untreated West syndrome can lead to significant developmental delays.[17]

Beyond the standard etiology: deciphering the potential role of vitamin b12 deficiency in infantile seizures

Pinpointing the culprit behind afebrile seizures, particularly those manifesting as infantile spasms (IS) in infants, can be a labyrinthine undertaking. While some forms of IS are readily treated and pose no long-term threat, achieving an early and accurate diagnosis remains paramount.

This not only facilitates the implementation of effective treatment but also circumvents the need for potentially superfluous and expensive examinations, along with the prolonged use of antiepileptic medications.

Intriguingly, recent research has unravelled a potential connection between vitamin B12 deficiency and IS in a specific subset of cases. Vitamin B12 acts as a maestro, orchestrating the intricate symphony of communication between brain cells within the nervous system. A deficiency in this crucial vitamin can manifest in a diverse array of neurological symptoms, with epilepsy being a rare but documented consequence in both adults and children.

The precise mechanism by which B12 deficiency contributes to seizures remains an enigma under active investigation. However, one compelling theory postulates that it might disrupt the protective sheath encasing nerve cells, known as myelin.

This damage could render these cells hypersensitive to the excitatory effects of glutamate, a key neurotransmitter in the brain. This heightened sensitivity may then trigger various seizure types, ranging from the brief, jerky movements characteristic of IS to full-blown generalized tonic-clonicseizures.[25-27]

Diagnostic challenges and sequelae of vitamin b12 deficiency in infantile seizures

While uncommon in developed countries, vitamin B12 deficiency can be a significant challenge in diagnosing and treating infantile seizures, particularly in exclusively breastfed infants born to mothers adhering to vegan diets.[13]

Atypical presentation and neurological manifestations

Unlike classic adult B12 deficiency characterized by megaloblastic anaemia, infantile cases often lack this hallmark sign.[28] Diagnosis is further complicated by the non-specific nature of neurological symptoms, including hypotonia, seizures, movement disorders, psychomotor regression and failure to thrive.[28,30]

A case of delayed diagnosis: highlighting potential consequences

The case study by Pin Fee Chong et al, exemplifies the deceptive nature of B12 deficiency in infants.[31] The infant exhibited hypomyelination and cerebral atrophy on MRI, potentially due to B12 deficiency during the crucial myelination period in the first six months of life. This period is critical for brain development, and deficiency can lead to irreversible neurological damage. While treatment improved MRI findings, earlier diagnosis might have prevented these complications.

Importance of early detection and differential diagnosis

This case highlights the potential consequences of delayed diagnosis, including earlier onset of West Syndrome (suggested by early developmental regression) and persistent developmental delay despite treatment. Clinicians must maintain a high index of suspicion for B12 deficiency, especially in exclusively breastfed infants presenting with failure to thrive, seizures or neurodevelopmental delays.[22] Differential diagnosis should include both genetic metabolic disorders and those acquired "environmentally" due to maternal deficiencies or autoantibodies.

Treatment landscape for infantile spasms:

Infantile spasms (IS) treatment aims for complete seizure cessation and normalization of the electroencephalogram (EEG) pattern (hypsarrhythmia) within a specific timeframe.[21] This article explores current therapeutic interventions and recent research advancements in IS management.

Vitamin B12 deficiency and treatment response

Since vitamin B12 deficiency can cause IS, close monitoring of exclusively breastfed infants with developmental delays or seizures is crucial for early diagnosis and treatment. Effective treatment for B12 deficiency typically leads to complete seizure resolution within 14 days of treatment initiation, with no recurrence within the following month.[21]

ACTH vs newer antiepileptic drugs (AEDs)

While adrenocorticotropic hormone (ACTH) remains a first-line therapy for IS, newer AEDs like zonisamide have shown promising results. Zonisamide exhibits a rapid response (1-2 weeks) with a success rate ranging from 20% to 38%.[23] Topiramate, another AED, has shown a lower response rate than ACTH (20-21%).[35,37]

Emerging therapies: mTOR inhibitor and nitrazepam

Recent research by Raffoet al, suggests the potential for mTOR inhibitors like rapamycin in treating ACTH-resistant IS in animal models. Nitrazepam, another medication, demonstrated seizure control in some cases but with a lower success rate (7 out of 20 patients).[21,23]

Pyridoxine and pyridoxal phosphate: conflicting evidence

While pyridoxine (vitamin B6) has shown limited efficacy in treating IS, Ohtsuka et al, reported a higher success rate (12 out of 118 patients) using high-dose pyridoxal phosphate, a B6 derivative.[25,35] Further research is needed to clarify the role of pyridoxine analogues in IS treatment.

CONCLUSION

This review meticulously unravels the enigmatic link between West syndrome, infantile seizures, and vitamin B12 deficiency. It weaves together diverse clinical cases with broader research findings, illuminating crucial aspects like the often-atypical presentation of B12 deficiency in infants, posing a "stealthy culprit" in diagnosis. Early intervention is paramount to prevent irreversible neurological damage. While ACTH remains a mainstay of treatment, the review explores promising alternatives and delves into the potential of mTOR inhibitors for treatment-resistant cases.

The diverse case studies presented here highlight the nuanced nature of this association, emphasizing the need for a comprehensive diagnostic approach that considers not only B12 deficiency but also cobalamin-related re-methylation disorders. This review is a valuable compass for paediatric neurologists navigating this intricate relationship. By emphasizing early identification, continuous monitoring, and a multi-pronged treatment approach, it guides them toward a more sophisticated approach. The future lies in continued research to further elucidate the underlying mechanisms and refine diagnostic technique.

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