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Subacute gestational neuropathy: role of thiamine deficiency

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Case #1

A 28-year old woman was admitted to our hospital at 5 months of a pregnancy complicated by daily vomiting. At 3 months of pregnancy, she started experiencing paresthesias in the lower limbs followed by progressive ascending weakness. Two weeks before admission in our hospital, while she was receiving a course of parenteral rehydration (IV solution unknown), she developed Wernicke encephalopathy (WE). She was given oral thiamine and pyridoxin and was transferred to our hospital. On physical examination, tachycardia and pitting oedema in the legs were noted. On neurological examination, she was disoriented. A bilateral horizontal gaze-evoked nystagmus was noted as well as flaccid paraplegia with weakness of the distal upper limbs, generalized areflexia and decreased sensation to all modalities in the lower limbs. Plantar responses were flexor. Tests for antinuclear antibodies, anti-neutrophil cytoplasmic antibodies, anti-ganglioside antibodies, cryoglobulin, HIV, hepatitis B and C virus, lead and urine porphobilinogen were all negative. Thyroïd studies, B12 and folate levels were normal. CSF studies were normal. Electrophysiological studies revealed a severe axonal sensory-motor polyneuropathy (Table 1). Brain MRI with FLAIR sequences demonstrated hypersignals in the medial thalamus and the periaqueductal gray matter, typical of WE (Fig. 1). She was given parenteral thiamine (300 mg daily) supplementation. At follow-up one year after discharge , she was ambulatory with a walking aid and was still recovering.

Case #2

A 24-year old woman was admitted to our hospital at 3 months of pregnancy complicated by daily vomiting. Ten days before admission, she started experiencing paresthesia in both feet that progressively

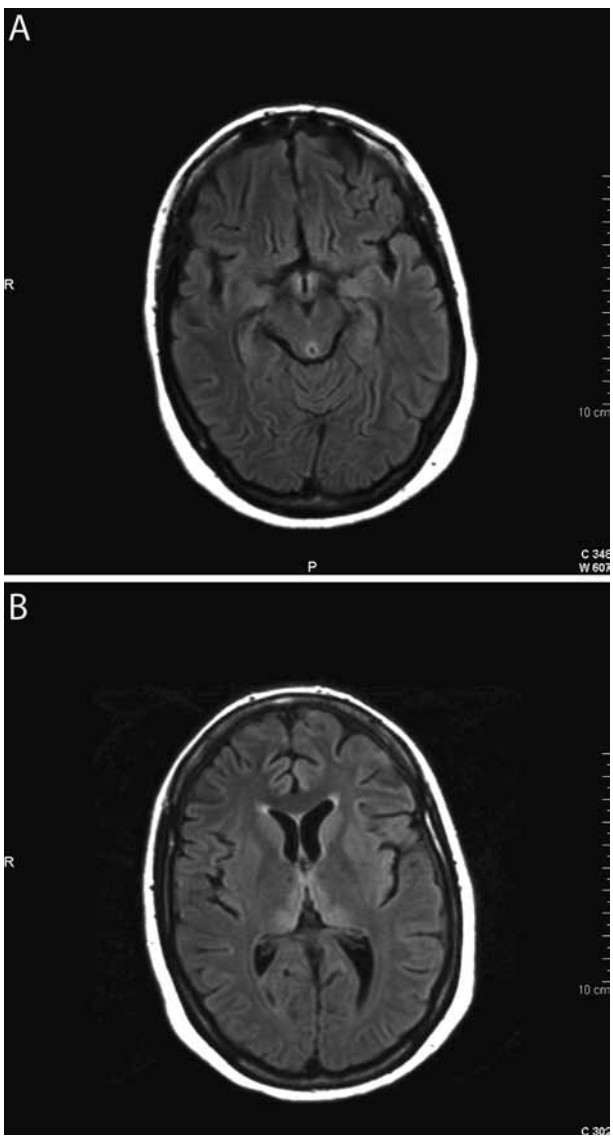

FIG. 1. — Brain MRI findings in patient 1
Axial fluid-attenuated inversion recovery brain MRI showing periaqueductal hypersignal.
Axial fluid-attenuated inversion recovery brain MRI showing bilateral medial thalamus hypersignal.

Table 1

Electrophysiological studies

Motor nerve conduction studies	**Patient 1**	**Patient 2**	**Ref Values**	**Demyelination criteria** (1, 2) Amp > 80%LLN		Amp < 80%LLN
Left peroneal nerve						
Distal latency	4	**13,1**	5,6ms	6,9ms		8,3ms
CMAP Duration	6,4	**17,1**	5,5ms		8,5ms	
CMAP Amplitude	**0,7**	**0,6**	2,8mV			
Velocity	46	43	40m/s	32m/s		28m/s
F-wave latency	**Absent**	**58,2**	56ms	67,2ms		84ms
Conduction block	No	No				
Right peroneal nerve						
Distal latency	4	**15,9**	5,6ms	6,9ms		8,3ms
CMAP Duration	5,1	**13,6**	5,5ms		8,5ms	
CMAP Amplitude	**0,1**	**0,6**	2,8mV			
Velocity	46	47	40m/s	32m/s		28m/s
F-wave latency	**Absent**	**67,4**	56ms	67,2ms		84ms
Conduction block	No	No				
Left tibial nerve						
Distal latency	5,2	**6,2**	6ms	7,5ms		9,0ms
CMAP Duration	2,7	**10,2**			8,5ms	
CMAP Amplitude	**2,9**	**2,1**	3,9mV			
Velocity	49	45	41m/s	32m/s		28m/s
F-wave latency	**Absent**	**62,6**	58ms	69,6ms		87ms
Conduction block	No	No				
Right tibial nerve						
Distal latency	5,5	**7,2**	6ms	7,5ms		9,0ms
CMAP Duration	4,1	6,7			8,5ms	
CMAP Amplitude	**2,9**	**1,9**	3,9mV			
Velocity	47	43	41m/s	32m/s		28m/s
F-wave latency	**Absent**	**58,8**	58ms	69,6ms		87ms
Conduction block	No	No				
Left median nerve						
Distal latency	2,7	**6,9**	4,1ms	5,3ms		6,3ms
CMAP Duration	4,2	**9,8**			8,5ms	
CMAP Amplitude	**11,6**	**1,2**	4mV			
Velocity	58,5	**47**	48m/s	38m/s		34m/s
F-wave latency	25,8	**38,1**	31ms	37,2ms		46,5ms
Conduction block	No	No				
Right median nerve						
Distal latency	2,8	**5,2**	4,1ms	5,3ms		6,3ms
CMAP Duration	5	**15,2**			8,5ms	
CMAP Amplitude	8,4	**1,3**	4mV			
Velocity	50	52	48m/s	38m/s		34m/s
F-wave latency	25,6	**38,1**	31ms	37,2ms		46,5ms
Conduction block	No	No				
Left ulnar nerve						
Distal latency	2,3	**5,9**	3,4ms	4,4ms		5,3ms
CMAP Duration	5,1	**9,6**			8,5ms	
CMAP Amplitude	5,4	**1,4**	3,7mV			
Velocity	59,8	65	48m/s	38m/s		34m/s
F-wave latency	27,2	30,6	32ms	38,4ms		48ms
Conduction block	No	No				
Right ulnar nerve						
Distal latency	2,4	**4,1**	3,4ms	4,4ms		5,3ms
CMAP Duration	5,1	**9,2**			8,5ms	
CMAP Amplitude	5,4	**2,8**	3,7mV			
Velocity	62,5	58	48m/s	38m/s		34m/s
F-wave latency	25,5	**33,3**	32ms	38,4ms		48ms
Conduction block	No	No				
Sensory nerve conduction studies						
Left sural nerve						
SNAP Amplitude	**Absent**	**Absent**	5,5mV			
Velocity	**Absent**	**Absent**	40m/s			
Right sural nerve						
SNAP Amplitude	**Absent**	**2,9**	5,5mV			
Velocity	**Absent**	42	40m/s			

Electromyography	**Patient 1**	**Patient 2**
Right tibialis anterior		
Insertional activity	**Increased**	**Increased**
Spontaneous activity	**Fibrillations and PSW**	No
MUPs	**No voluntary contraction**	Normal
Maximal exertion	**No voluntary contraction**	**Intermediate**

Abnormal values are in bold and criteria for demyelination are underlined; CMAP: compound motor action potential, SNAP: sensory nerve action potential, LLN: lower limit of normal.

ascended to the legs and fingers, followed by leg weakness. On neurological examination, gaze-evoked nystagmus was present but ocular motility was full. She had a flaccid paraparesis, more prominent in the extremities with areflexia in the legs and decreased sensation to tactile, painful stimuli as well as pallesthesia in both feet. Plantar responses were flexor. She was unable to walk without assistance.

Electrophysiological studies revealed a severe axonal sensory-motor polyneuropathy with increased distal latencies and CMAP duration in more than two tested nerves (Table 1), suggesting an associated demyelinating process (1, 2). These findings led us first to consider a variant of Guillain-Barré syndrome but blood and CSF studies were normal, including absence of anti-ganglioside antibodies and normal CSF protein level. Brain MRI was normal. She was given parenteral thiamine (1500 mg daily) supplementation and was able to walk after a few days. She was discharged from the hospital against medical advice and transiently lost to follow-up. She was seen again after three months and had made a full recovery at that time.

Discussion

Thiamine deficiency might result from insufficient intake or increased metabolic states (staple polished rice diet, chronic alcohol abuse, malnutrition, gastrointestinal surgical procedures, chronic diarrhoea, cancer, systemic disease) (3) and can provoke a slowly progressive axonal polyneuropathy. A subacute form of polyneuropathy has also been occasionally described in different clinical settings (4-9) but was only reported once in relation to hyperemesis gravidarum (10).

Our two cases illustrate that hyperemesis gravidarum can lead to a severe subacute axonal neuropathy and strongly suggest that the aetiology is thiamine deficiency. Although we did not directly measure thiamine status, the careful exclusion of all other causes of subacute neuropathy, the association with Wernicke encephalopathy and wet Beri-Beri and the recovery upon thiamine supplementation support this conclusion.

Other vitamin deficiencies, such as pyridoxin and cobalamin, can cause a peripheral neuropathy and may also have been implicated but this is unlikely. Pyridoxin deficiency rarely causes a severe motor neuropathy as seen in our cases and the associated mucous and cutaneous signs were absent (11, 12). Cobalamin deficiency usually leads to a chronic myelopathy or combined myeloneuropathy, but rarely to an isolated peripheral neuropathy (13, 14). Although a mild myelopathy can not be ruled out in our cases, frank signs of combined degeneration of the spinal cord, such as extensor plantar responses, were missing. Furthermore, despite excellent outcome, neither patient received cobalamin supplementation.

In addition, both patients were following a pork-free diet. As pork is one of the richest source of thiamine (3), this specific diet might have put them at greater risk of developing thiamine deficiency.

Of interest is the major difference in evolution between the two patients. The first patient developed a "classic" carential neuropathy: symptoms evolved progressively over a period of weeks, electrophysiological studies suggested purely axonal pathology and recovery was slow, as expected when axonal regrowth has to take place. On the other hand, the second patient had a more acute course and electrophysiological studies were more equivocal with some findings suggestive of demyelination or at least alteration of nerve conduction in the distal axonal segments. Although we initially suspected an acute inflammatory demyelinating polyradiculoneuropathy, the extent of the sensory involvement and results from ancillary tests argued against this diagnosis and the patient made a surprisingly rapid recovery upon thiamine supplementation. Others have already reported on such rapid recovery in similar cases, correctly pointing out the fact that axonal regeneration could not explain it (5). Alternative mechanisms must then be considered. It is first possible, as our electrophysiological studies suggest, that conduction blocks due to demyelination occurred in the distal axonal segments. In this line, some animal studies have shown disorganization of the myelin sheets in acute thiamine deprivation (15) and thiamine acts as a co-factor for the transketolase enzyme which is involved in myelination (16). Another possible mechanism is degeneration of the distal intramuscular axonal segments, as seen in acute motor axonal neuropathy (AMAN), after which recovery is usually quick, owing to the short period of time required for regeneration of nerve terminals (17). In addition to distal axonal loss and/or demyelination, reversible functional conduction failure should be discussed. Interestingly, thiamine has been detected in nerve membranes and it is suggested to control the number of functioning ion channels in the nodes of Ranvier (18). Anti-GM1 antibodies found in AMAN and experimental autoimmune neuropathy have been shown to disrupt the cellular organization of nodes of Ranvier and to interfere with Na_V channels clustering and function, leading to conduction slowing and block (19). It is thus conceivable that similar functional conduction blocks also occur with thiamine deficiency before

axonal or myelin degeneration happen. Thiamine is also a co-factor for the pyruvate dehydrogenase (PDH) enzyme, a critical component in cell energetic metabolism. Thiamine deficiency leads to a decrease in PDH activity and in ATP levels which compromises NA+-K+-ATPase activity and may interefere with the maintenance of peripheral nerve depolarisation and axon excitability, further hampering conduction (20). Which of these mechanisms alone or in combination are responsible and why they are restricted to distal axonal segments remain unexplained.

Conclusion

Subacute neuropathy during pregnancy is rare. Thiamine deficiency should be considered as a possible aetiology in pregnant women with a history of hyperemesis gravidarum, especially if they follow a restricted diet. As methods to assess thiamine status are not routinely available, the diagnosis of this uncommon complication must be made on clinical grounds alone to ensure early treatment and full recovery. Thiamine deficiency might alter the function of peripheral nerves through various mechanisms.

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