

Thiamine deficiency-induced gestational polyneuropathy and encephalopathy

A case report

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Summary

A 22-year-old multigravida presented with polyneuropathy and encephalopathy at 18 weeks' pregnancy. After excluding other applicable conditions, the diagnosis of a hyperemesis-induced thiamine deficiency was made. With the necessary vitamin supplementation the patient gradually recovered over a period of 4 months and was delivered of a normal infant at term. Gestational polyneuropathy and encephalopathy due to thiamine deficiency has very rarely been reported. The literature is reviewed with discussion of the differential diagnosis, the treatment and the prognosis.

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Pregnancy is a physiological state accompanied by an increased requirement of all nutrients. Iron and folic acid supplementation in pregnancy is considered standard practice. However, other nutritional deficiencies may develop, particularly in pregnancies associated with complications which entail diminished food intake. We report on a patient who developed thiamine deficiency at the clinical level because of inadequate food intake due to vomiting.

Case report

A 22-year-old multigravida was referred to Tygerberg Hospital from a smaller hospital nearby after admission there in a state of mental confusion and with a working diagnosis of septic abortion.

The history obtained from her family revealed that the patient was again pregnant, that she had 3 children living and that she was not attending an antenatal clinic. Over a period of about 2 months she had developed progressively worsening weakness, which had started in the lower limbs and spread to

the upper limbs. This had been preceded by tingling and pain in the feet. The patient could not walk and could only stand with great difficulty on admission. Her family had also noted periods of forgetfulness and mental confusion in the week preceding admission; they thought she had been poisoned. After specific questioning an important fact was elicited. The patient had suffered persistent vomiting (an average of four episodes per day) over the previous 3 months, for which she had consulted her general practitioner. It was established that during this period the patient's dietary intake had consisted exclusively of iced water, sugared tea or coffee (6 cups daily with 3 tablespoons of sugar per cup), Oxo-cube soup (made with water 3 times daily), and custard (made with sugar and fresh milk, twice daily). In the week before admission to Tygerberg Hospital the patient had developed a mild fever for which she visited the referring hospital.

On clinical examination the patient was apathetic, wasted, confused and severely dehydrated. Angular stomatitis, magenta coloration of the tongue and papillary atrophy were present. The heart rate was 130/min, temperature 37,8°C and blood pressure 110/70 mmHg. No retinopathy was visible on funduscopy. Abdominal examination revealed a non-tender uterus the size of an 18-week pregnancy; a normal fetal heart rate was detected with Doppler ultrasound. The patient's heart size was within normal limits and, apart from tachycardia, a hyperdynamic pulse was present as well as an ejection systolic 2/6 murmur localized over the pulmonary area.

Neurological examination revealed apathy, clouding of consciousness and disorientation for place, time and person; horizontal nystagmus to the left and right and an impression of bilateral facial weakness. There was drop-foot on the right and flaccid paralysis of both legs except for a slight degree of power present in the thigh muscles. The arms were similarly involved but to a lesser degree, the weakness being more pronounced distally than proximally. The patient could not sit up without help. With the exception of touch, all specific sensory modalities were diffusely impaired in the lower limbs and to a lesser extent in the upper limbs. A striking feature was marked hypersensitivity on touch and severe pain on deep pressure of the calf muscles. The deep tendon reflexes were absent and the plantar response was bilaterally flexor. Cerebellar signs were unreliable because of the patient's weakness.

The only abnormality found on gynaecological examination was a slightly offensive vaginal discharge; cytological examination suggested *Gardnerella vaginalis*.

The following were normal: white cell and platelet counts; serum electrolyte, creatinine, phosphate and creatinine kinase levels; blood glucose level; chest radiograph; toxicology screening; Wassermann reaction; collagen screening; thyroid function tests; urine screening for porphyria; and serum vitamin B₁₂ and serum folate levels.

Abdominal ultrasound examination revealed a normal 18-week pregnancy.

The results of the following special examinations were abnormal: haemoglobin 9,0 g/dl with a normochromic, normocytic blood smear; erythrocyte sedimentation rate (ESR) 100

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mm/1st h (Westergren); serum urea level 11,6 mmol/l (normal 3,3 - 6,5 mmol/l) (in view of the normal serum electrolytes and creatinine values this was indicative of a prerenal uraemia); serum calcium level 1,93 mmol/l (normal 2,1 - 2,6 mmol/l) (corrected for low serum albumin the calcium value was, however, well within normal limits); serum magnesium level 0,54 mmol/l (normal 0,75 - 1,5 mmol/l); pH and blood gases indicative of metabolic alkalosis with respiratory compensation; liver function tests — low serum albumin (28 g/l) with normal globulin, hyperbilirubinaemia (33 μ mol/l) with 17 μ mol/l unconjugated; all liver enzyme values were slightly disturbed (lactate dehydrogenase 421 U/l (normal 100 - 350 U/l), aspartate aminotransferase 82 U/l (normal 0 - 40 U/l), alanine aminotransferase 59 U/l (normal 0 - 53 U/l), alkaline phosphatase 104 U/l (normal 30 - 85 U/l), γ -glutamyl transpeptidase 83 U/l (normal 0 - 50 U/l). An ECG showed sinus tachycardia with diffuse nonspecific T-wave flattening; and the electromyographic findings were indicative of an axonal polyneuropathy with fibrillations and pseudomyotonic reactions in the long extensor muscle of the toes during rest, and broad polyphasic potentials on contraction in all the leg muscles examined. The motor and sensory conduction velocity in the median nerves was normal, as was the sensory conduction velocity in the peroneal nerves; there was a slight slowing of the F wave in the peroneal nerves.

Management and course

Strict bed rest was instituted and the patient was rehydrated with 5% dextrose-saline. The *Gardnerella* vaginitis was treated with ampicillin and metronidazole. Intramuscular prochlorperazine mesylate was prescribed for the persistent vomiting. However, despite complete rehydration and return of the temperature to normal, the patient's level of consciousness and overall neurological picture deteriorated over the next 24 hours. Additional therapy was instituted in the form of vitamin B complex (2 ampoules per Vacoliter Maintelyte 8-hourly), thiamine 100 mg intramuscularly followed by 50 mg daily for the next 10 days, and restriction of oral carbohydrate.

The patient's encephalopathic symptoms disappeared over the next 48 hours and an electro-encephalogram 3 days after the start of thiamine therapy was normal. The tachycardia resolved spontaneously and an increase in diastolic pressure of 20 mmHg was noted. The disturbed liver functions returned to normal within the next 7 days. The increased ESR returned to normal pregnancy values within a few days. The polyneuropathic picture also improved dramatically initially, but on discharge 10 days later the patient was still confined to a wheelchair. Over a period of 4 months and with the aid of physiotherapy she gradually returned to full mobility. The patient took oral vitamin B complex, folic acid and iron daily for the rest of her pregnancy. No further vomiting occurred and her haemoglobin level returned to normal.

At term the patient went into spontaneous labour and was delivered of a normal female infant weighing 2840 g, with an Apgar score of 9 at 1 minute, 10 at 5 minutes and 10 at 10 minutes. The placenta was normal.

Differential diagnosis

The differential diagnosis in this case is that of a pregnant woman with persistent vomiting, polyneuropathy and encephalopathy. Porphyria, which is not uncommon in South Africa, can present with a similar clinical picture and is known to worsen during pregnancy.¹ The specific screening test was, however, negative. Diabetes mellitus was excluded by the finding of a normal blood glucose level and other metabolic conditions were excluded by the presence of normal serum

electrolyte, normal corrected serum calcium and normal serum phosphate values.

Because the patient's history included the possibility of poisoning, comprehensive toxicology screening tests were done but all were negative. Ethanol and methanol blood levels were also zero and no history of excessive alcohol intake could be obtained. Systemic lupus erythematosus (SLE) had to be excluded because it can cause clouding of consciousness with a psychotic picture and polyneuropathy.² There was, however, no evidence of systemic vasculitis and tests for LE cells, antinuclear factor and anti-DNA were negative.

Having excluded most conditions known to cause a polyneuropathy, the diagnosis of thiamine deficiency-induced polyneuropathy and encephalopathy caused by hyperemesis of pregnancy was made.

It is well known that a deficiency of one type of B vitamin may be accompanied by deficiencies of other B vitamins. The plasma vitamin B₁₂ concentration was normal and the clinical symptoms and signs of pellagra were absent, although a biochemical deficiency of the latter cannot be excluded. Specific tests for pyridoxine and riboflavin deficiency were not done and a degree of concomitant deficiency can therefore not be excluded. Indeed, the magenta coloration of the tongue would be compatible with the latter. However, the patient's deterioration when glucose was administered, the overall clinical picture, and the rapid and dramatic response to thiamine treatment combined with the carbohydrate restriction favours the diagnosis of thiamine deficiency. Indeed, the correct diagnosis was first suspected after her deterioration following the intravenous dextrose-saline therapy. In retrospect this initial therapy had been incorrect. Furthermore, the daily thiamine requirements must have been specifically increased in this patient in view of her dietary intake over the last 3 months, which consisted almost exclusively of carbohydrate with practically no vitamins.

It is well known³ that thiamine requirements are related to carbohydrate intake, and this may explain the earlier clinical manifestation of thiamine deficiency rather than of deficiencies of the other B vitamins. Laboratory confirmation of the deficiency (transketolase activity and thiamine pyrophosphate (TPP) was not possible, since these could unfortunately only be determined after the patient had already received more than 48 hours of thiamine treatment, because she was admitted just before a weekend. When the transketolase activity and TPP effect were determined on the 3rd and 5th days after starting thiamine treatment, they were found to be normal (63 U/l, TPP effect 5,3%; 62 U/l, TPP effect 6,7% respectively; normal range: 30 - 50 U/l, TPP effect < 25%). The higher than normal levels of activity can be attributed to the high doses of thiamine used for supplementation.

Discussion

Gestational polyneuropathy was first reported in the literature by Churchill⁴ of Dublin in 1854. In 1890 Tuillant⁵ suggested that the condition was due to a lack of nourishment following persistent vomiting. Despite this, hysteria and auto-intoxication were for many years the favoured aetiological factors. In 1930 Theobald,⁶ working in Bangkok, suggested that the neuritis of pregnancy was due to a vitamin B deficiency in view of the fact that beri-beri was twice as common in pregnant as in non-pregnant women. In 1933 Strauss and McDonald⁷ reported 3 cases cured by vitamin B supplements.

The encephalopathy of thiamine deficiency is also known as Wernicke's encephalopathy⁸ and, when associated with psychosis, as the Wernicke-Korsakoff syndrome.⁹ This syndrome is more commonly associated with the thiamine

deficiency of chronic alcoholism. Wernicke described the encephalopathy associated with his name as acute superior haemorrhagic polio-encephalitis, and later Korsakoff described the frequently associated psychosis. The association between Korsakoff's psychosis and Wernicke's encephalopathy was not made until 1901 by Bonhoeffer (quoted by Campbell and Biggart¹⁰). Korsakoff himself called attention to the association of this syndrome with pregnancy with a case report in 1892,¹¹ but it was only in 1932 that Berkwitz and Lufkin¹² firmly defined the syndrome during pregnancy, describing it as toxic neuronitis of pregnancy. The association between these syndromes and vitamin B₁ deficiency was pointed out by Strauss¹³ in 1938.

Although any form of polyneuropathy may occur in pregnancy,¹⁴ it is usually due to thiamine (vitamin B₁) deficiency resulting from a number of factors.¹⁵ Thiamine, in common with other water-soluble vitamins, is not stored in large amounts in the body. Reserves will therefore become exhausted within a few months if the daily requirement of 1 - 2 mg is not available from food, because the vitamin cannot be synthesized in the human body.¹⁵ The increased metabolic rate in pregnancy and fetal demands necessitate a doubling or tripling of the normal daily intake to about 3 - 5 mg.¹⁵ Williams *et al.*¹⁶ in 1940 found that more than 30% of normal pregnant women had an inadequate intake of thiamine. The increased incidence of vomiting in pregnancy may also precipitate the condition, and the majority of cases reported in the literature have either been associated with hyperemesis gravidarum or occurred as one of its complications.¹⁵

There are two main clinical syndromes of thiamine deficiency, namely wet beri-beri (involving mainly the cardiovascular system) and dry beri-beri (involving mainly the nervous system). Usually the clinical picture is a mixture of the two but pure forms do occur. The usual clinical setting for the development of thiamine deficiency is generally thought to be alcoholism and chronic malnutrition. The association of these syndromes with pregnancy is less well known, and the full-blown clinical picture, as seen in our patient, is rare.

The classic clinical description by Agnew and Vancouver¹⁷ in 1946 of this syndrome overlaps almost completely with the clinical findings in our patient. The main symptoms are tingling, numbness, and sometimes pain in the hands and feet. There is a history of persistent vomiting and patients are often labelled neurotic. The numbness may lead to inco-ordination and difficulty in picking up small objects. Periods of forgetfulness and mental confusion may add to the suspicion of neurosis. Muscle weakness becomes more prominent and initially involves mainly the distal extremities, spreading centrally. The abdominal muscles, the rectum and the bladder may be involved in severe cases. Later the full picture of Wernicke's encephalopathy may develop. This is characterized by ocular disturbances such as nystagmus (horizontal nystagmus being more common than vertical), ataxia and derangement of mental function.⁹ Unilateral or bilateral facial nerve palsy or palsies of other cranial nerves may rarely occur.¹⁸ Optic neuritis and retinal haemorrhages are the main fundoscopic signs. The most common cardiovascular abnormality is a persistent resting tachycardia, and this and cardiac dilatation are said to be ominous signs.¹⁵ The cause of death is usually cardiac failure or paralysis of the respiratory muscles. If recovery occurs it is slow but usually complete. The central nervous system signs disappear over days but the polyneuropathy recovers over a period of 3 - 18 months, depending on the degree of damage to the peripheral nerves. A few cases of permanent paralysis have been reported.¹⁷

The clinical picture of thiamine deficiency can be explained by the vitamin's role as a co-enzyme in neuronal function and intermediary metabolism. The enzymatic reactions of importance are the oxidative decarboxylation of α -keto acids

and keto analogues of leucine, isoleucine and valine, and the transketolase reaction in the pentose phosphate pathway.¹⁹ Measurement of whole blood or erythrocyte transketolase activity has therefore been recommended as a specific and sensitive method of determining thiamine deficiency.¹⁹ There is, however, wide individual variation and absolute activity, unless markedly depressed, is in general not as useful an indication as is an increase in activity with treatment.¹⁹ Another criterion for the diagnosis of thiamine deficiency is the assessment of the clinical response to thiamine administration,¹⁹ which is associated with slow but progressive improvement in neurological deficits, resolution of existing tachycardia and transient relative hypertension — a response seen in our patient.

Treatment consists of the prompt administration of thiamine on suspicion of the diagnosis. Fifty milligrams given intramuscularly daily for several days, followed by 2,5 - 5 mg orally per day for a month is the recommended therapy.¹⁹ Large oral doses are not absorbed. Thiamine may also be added to the intravenous fluids. Other B-vitamin supplements should be added to the treatment, since thiamine deficiency seldom occurs alone. It is important to realize that the administration of carbohydrates such as glucose without the simultaneous administration of thiamine may precipitate acute Wernicke's encephalopathy or worsen signs of existing encephalopathy, as in our patient. In patients with hyperemesis gravidarum parenteral vitamin B₁ therapy should continue until the vomiting subsides, since vomiting itself is a symptom of thiamine deficiency,³ and this may form a vicious circle which, once established, leads to rapid deterioration in the patient's condition.

The prognosis for thiamine deficiency in pregnancy is grave if specific treatment is not given. McGoogan²⁰ found that of 105 patients who received no thiamine 35,2% died, but among 40 treated with the vitamin the mortality rate was 7,3%. Because of the rarity of the full-blown condition there is a lack of recent reports in the literature on the prognosis of gestational encephalopathy due to thiamine deficiency. It would, however, appear to be grave condition, death occurring in 15 - 20% of hospitalized non-pregnant patients with this disease.⁹ If Korsakoff's psychosis is present, complete or almost complete recovery occurs in only 20% of patients.⁹

The specific effects of thiamine deficiency on the fetus are not completely known. It may be associated with abortion, and in rats it has been found to be responsible for fetal resorption but not for malformations.²¹

Conclusion

Gestational polyneuropathy with encephalopathy due to thiamine deficiency is rare but serious and is usually precipitated by persistent vomiting. Because of its rarity the diagnosis can be easily missed, with possible fatal results for the patient and her unborn baby. A high degree of awareness is therefore necessary in the right clinical setting.

Because of the grave prognosis for untreated cases prompt initiation of the correct therapy is imperative. Mortality appears to be high even with treatment in severe cases, although the outlook for complete recovery is excellent in mild cases after prompt treatment. It may therefore be considered desirable to administer multivitamin supplements to pregnant women with a history of persistent vomiting, particularly in view of the frequent coexistence of deficiencies of the B vitamins. The administration of dextrose infusions without the concomitant administration of thiamine would appear detrimental and should be avoided.

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Intra-ocular tuberculosis associated with a penetrating injury

A case report

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Summary

A case of histologically proven intra-ocular tuberculosis is described. The condition was preceded by penetrating trauma, and no evidence of systemic tuberculosis other than a positive Mantoux test was found. Numerous acid-fast bacilli were seen in pathological sections of the eye. We suspect that a tuberculosis bacillaemia from an undetected healed focus coincided with the trauma and thereby produced intra-ocular tuberculosis.

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Case report

In September 1982 the patient, a 9-year-old black schoolboy, sustained a penetrating injury when poked in the left eye with a needle by a playmate. Medical advice was not initially sought. Although at first no symptoms were apparent, by December 1982 the eye was painful and blind; it was enucleated in January 1983. Both eyes had previously been symptom-free, and there were no signs or history of tuberculosis.

On examination of the enucleated eye the eyeball measured 30 x 25 mm. Occupying the anterior portion and surrounding the lens was firm white tissue measuring 15 x 15 x 10 mm. Microscopy showed confluent granulomas (Fig. 1) made up of epithelioid cells and Langhans' giant cells, and an inflammatory cell infiltrate including lymphocytes and plasma cells (Fig. 2). There were also foci of necrosis. Numerous acid- and alcohol-fast bacilli were seen on Ziehl-Neelsen staining, confirming the diagnosis of tuberculosis.

After this somewhat surprising pathological report had been received, the patient was readmitted for investigation. On examination he appeared well and free of respiratory disease, although his body mass (22,6 kg) was below the 10th decile. The left socket had healed well, but in the right eye a mild

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