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Neurocirculatory Manifestations of Thiamine Deficiency

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Abstract

The diagnosis of thiamine deficiency is essentially made on clinical grounds and may present with neurological deficit such as peripheral neuropathy and Wernicke's encephalopathy, or with high output heart failure (wet beriberi). This study was done to determine the frequency with which both the neurological and cardiovascular manifestations coexist in states of thiamine deficiency.

The hospital records of 186 patients admitted on 200 occasions with a diagnosis of thiamine deficiency due to beriberi or Wernickes encephalopathy were reviewed during the 7-year period (1994-2000). Cases were only included in the analysis if mental changes and neurological deficit (opthalmoplegia, ataxia, nystagmus) resolved rapidly after treatment with thiamine. Similar to the neurological recovery with thiamine, a rapid response in the cardiovascular state and in the metabolic acidosis to treatment with parenteral thiamine was taken as confirmatory evidence of thiamine deficiency.

In all but 11 patients, complete recovery ensued within 1-3 days of treatment with parenteral thiamine. The 175 patients who responded dramatically to thiamine (67 Wernicke's encephalopathy and 108 cardiac beriberi) form the subject of this review. In total, 43/175 (25%) patients exhibited combined neurologic and circulatory manifestations of thiamine deficiency. Eighteen patients presented with overt coexisting neurocardiac manifestations, twelve of whom had acute pernicious beriberi with circulatory shock, metabolic acidosis and accompanying neurological deficit. There was one death due to circulatory shock and metabolic acidosis in patient who arrived in extremis with an unrecordable blood pressure at the emergency room.

Cardiovascular/circulatory manifestations in patients presenting with acute neurological deficit are not infrequent and should raise suspicion of thiamine deficiency. Likewise patients with advanced thiamine deficiency states presenting with shock and metabolic acidosis not infrequently have coexistent signs of WE. Empiric therapy with thiamine in advanced stages of thiamine deficiency is life-saving and a rapid therapeutic response is confirmatory of the diagnosis.

Keywords: Thiamine deficiency; Neurocardiac; Neurocirculatory; Wernicke's encephalopathy; Shoshin; Metabolic acidosis

Introduction

Thiamine deficiency may present clinically as Wernicke's encephalopathy (dry beriberi) or with symptoms of high output failure (wet beriberi). Whether the presenting features are neurological or cardiovascular the presumptive diagnosis of thiamine deficiency is essentially made on clinical grounds. Biochemical assays of thiamine status offer diagnostic confirmation of thiamine deficiency provided however, that blood samples are estimated prior to the initiation of treatment. Treatment delay is unwise in subjects who develop complications such as low output failure, particularly the low output Shoshin type, and in Wernicke's encephalopathy because of the risk of irreversible deficits and death. These conditions therefore dictate empiric therapy with thiamine and a therapeutic response is confirmatory of the diagnosis.

In its classic form Wernicke's encephalopathy (WE) is a neurological disorder of acute onset, characterised by the triad of ocular palsy, ataxia and a global confusional state [1,2]. Unfortunately, the classical triad is neither consistently nor frequently encountered and the onset of the syndrome may evolve over several days [1,2], Furthermore, several studies have confirmed the fact that Wernicke's encephalopathy (WE) is poorly recognised, even when features of the classic triad are evident [1,2]. Recognition of the progressive nature of the disease is critical since untreated the mortality rate is 10-20% and treatment may correct all the abnormalities (ref). Therefore a high index of suspicion is necessary in the early diagnosis of Wernicke's encephalopathy.

Furthermore, in heart failure, a hyperdynamic state may often be attributable to coexistent fever and anaemia which commonly precipitate heart failure in patients with reduced myocardial reserve. This may mask the underlying thiamine deficiency state, leading to delay in diagnosis and treatment. The presence of coexistent neurological and circulatory clinical features may therefore be useful in making a presumptive diagnosis of thiamine deficiency at presentation so that appropriate therapy with thiamine may be instituted timeously.

However, it has long been thought that cardiovascular beriberi and Wernicke's encephalopathy do not co-exist. Indeed, for many years cardiac manifestations of thiamine deficiency have been noted to be an unusual accompaniment in Wernicke's encephalopathy [3-6]. In a series of 86 patients with Wernicke's encephalopathy reported more

than 45 years ago only one manifested the advanced signs of beriberi heart disease. Cardiovascular symptoms and signs of heart failure were notably absent. Furthermore, patients with WE often present with a disturbance of mental state and are unable to give an adequate history. Even later, during recovery, a history of cardiovascular symptoms is often wanting due to the development of the amnesic syndrome. In our own experience the presence of neurological and cardiac symptoms and signs are not mutually exclusive. Seven out of thirty-six cases of WE were noted in a previous report from our institution to have cardiovascular symptoms and/or signs [7]. We therefore performed a retrospective study that evaluated the co-existence of cardiovascular and neurologic manifestations among patients admitted due to cardiovascular instability and/or WE to determine the pattern of presentation in patients presenting with thiamine deficiency states.

Method

The hospital records of all patients diagnosed as cardiac beriberi or Wernicke's encephalopathy admitted to King Edward VIII Hospital, a tertiary level general hospital, during 1994-2000 were reviewed. A search in the registry database of the hospital was performed using the CDC codes for thiamine deficiency, beriberi and Wernicke's disease. Although it is now recognised that the triad of mental confusion, ataxia and opthalmoplegia are seldom present together, in the majority of cases the diagnosis of Wernicke's encephalopathy rested on the identification of these clinical criteria. Cases were only included in the analysis if mental changes and neurological deficit (opthalmoplegia, ataxia, mystagmus) resolved rapidly after treatment with thiamine [6]. Cardiac beriberi was diagnosed when signs of cardiac failure were associated with a high output state. The diagnosis of shoshin or acute pernicious beriberi was made when cardiovascular collapse was accompanied by severe metabolic acidosis. Similar to the neurological recovery with thiamine, a rapid response in the cardiovascular state and in the metabolic acidosis to treatment with parenteral thiamine was taken as confirmatory evidence of thiamine deficiency. Thiamine status, as determined by red blood cell transketolase and the pyrophosphate effect provided biochemical evidence of thiamine deficiency in only a few instances where the blood sample was assayed prior to treatment with thiamine and have not been included in this analysis.

Results

A total of 186 hospital patients admitted on 200 occasions were reviewed during the 7-year period. Eleven patients were excluded because clinical features persisted after thiamine therapy. The remaining 175 cases comprised 67 with a clinical diagnosis of Wernicke's encephalopathy and 108 as cardiac beriberi. At admission no patient exhibited tremor and/or agitation which would have suggested an alcohol withdrawal state; nor was there evidence of acute alcohol intoxication, so that the clinical picture with its acute response to thiamine could be ascribed almost entirely to the thiamine deficiency state.

Chronic alcoholism with its accompanying dietary deficiency was the common underlying predisposing factor in the entire group. Most subjects were young adult men and generally appeared well-nourished with preserved albumin and hemoglobin levels, but had a strong history of excessive alcohol intake as suggested by the elevated MCV and hepatitic picture of the liver function tests. Severe avitaminosis with weight loss, however, was noticed in only 8 subjects.

Wernicke's encephalopathy with coexisting cardiovascular alterations

Definite coexistent cardiovascular signs and symptoms indicating beriberi heart disease were documented in eighteen of the sixty-seven (27%) patients with Wernicke's encephalopathy. The coexisting clinical features in these eighteen cases are summarised in Table 1. Amongst these, nine patients presented with heart failure and/or metabolic acidosis and the remaining nine had a predominantly neurologic presentation. Of the nine with severe cardiovascular changes, seven had severe metabolic acidosis. Cardiogenic shock was an accompanying feature in five of these seven subjects. The triad (opthalmoplegia, ataxia, mental changes and nystagmus) of Wernicke encephalopathy was present in five of this group with a cardiovascular presentation.

No	Age	Presenting features	Coexisting findings	BP	HCO_3-Mmol/l	Other lab results/ECG
Neurologic						
1	38M	Seizures, Hypothermia	WE	130/80	14	U&E showed low HCO3
5	60M	Mental changes, ataxia, nystagmus	WE	120/70		
12	34M	ophthalmoplegia	WE	130/70		
9	56M	WE		140/70		T wave € on ECG
3	52M	Ophthalmoplegia.	WE	120/80		ECG showed T-wave inversion
10	30F	WE + Pellagra. .	HF	120/60		
11	40M	WE	HF	140/95	15	γGT 178; BS 11.8mmol/l
17	50M	Lower limb weakness, mentally dull, Bilateral ptosis, Opthalmoplegia, peripheral N, Gait ataxia	HF, Chest pain, MA	100/60		

18	36M	Confusion, left VI N palsy, Nystagmus ataxia,	Pistol shots & femoral bruit	140/70		
Cardiovascular						
14	26M	Heart failure and Metabolic acidosis	WE + PN.	130/50	4.4	γGT 117 MCV100 BS 10.4
15	76M	Heart failure and Metabolic acidosis		120/70		BE –27, Lactate 22.9 mmol/l.
6	50F	Heart failure and Metabolic acidosis	Ataxia, Peripheral neuropathy and proximal myopathy	120/70	17.8	MCV 101 γGT 196 AST 203
16	46F	Cardiogenic shock + Metabolic acidosis	Pain & weakness in LL, peripheral Neuropathy	60/0		
2	60F	Cardiogenic shock + Metabolic acidosis	WE	80/60	5.7	pH 7.17, BE – 10.5, MCV 104
7	40M	Cardiogenic shock + Metabolic acidosis	During recovery : WE, PN and hepatitis	80/40	8.5	pH 7.27, BE –15. γGT 56 AST 138
4	35M	Circulatory shock + Metabolic acidosis Ophthalmoplegia	WE	60/0	14	pH 7.21 BE –15, MCV 82 γGT 109 AST 64
13	36M	Heart failure Cardiogenic shock + Metabolic acidosis	Hepatitis, Ataxia, Nystagmus	Not recordable	3.4	pH not done γGT 596 AST 1305 MCV106
8	58M	Heart failure Cardiogenic shock + Metabolic acidosis	WE on recovery	70/30	4.4	

Table 1: Coexisting neurocardiac manifestations of thiamine deficiency

Of the nine who had a predominantly neurologic presentation with Wernicke's encephalopathy, five had signs of high output failure and a further two showed ECG changes of significant t wave inversion. The remaining two had severe metabolic acidosis, one of whom was in cardiogenic shock. Blood pressure readings revealed a hyperdynamic state with a wide pulse pressure in six subjects.

A review of the blood pressures in subjects diagnosed as Wernicke's revealed that in a further twenty-five patients clinical evidence of a high output state was not recorded in the patients' charts, but the blood pressure recordings showed wide pulse pressures of at least 50mmHg in these subjects (37%). In this group, although not documented, there was evidence of a metabolic acidosis that was clearly present as identified by the laboratory serum electrolyte estimation which showed a low serum bicarbonate level in 10/25 (40%) subjects from the (Table 2).

	Age	BP	HCO_{3-}	Urea	Cr	Alb	Bili	γGT	AST	MCV	Hb	B/S
ZM	38M	130/80	15.9	4.8	95	40	12	95	75		12.1	
WJ	60M	100/70	24.5	6.3		36	116	49	28	88	11.0	
LS	50M	140/70	31.8	2.2	81	38	8	38			13	5.1
TK	30F	120/60	19	4.9	85	30	37	230		97	10.7	6.4
SM	40M	140/95	15	7.4	111	38	36	179				
SN	34M	130/70	19.9	11.8	91	42	12	42			12.7	10.6
MM	26M	130/50	20	7.5	135	41	26	326	45	98		7.1

EM	35M	130/80	16.2	4.2	91	44	24	19	26	106	13.8	6.6
LM	40M	120/70	13.3	5.6	91	33	13	50	36	81	12.2	6.4
LZ	43M	110/60	11.0	19.6	199	48	21	86			4.5	6.2
BM	43M	140/80	14.7	3.4	82	41	24	177		106	12.7	4.3
SM	48M	140/90	14.4	4.4	124	37	13	37		89	13.7	5.6
MN	34M	120/80	16.5	13	159	37	29	269		79	20	20.2
IS	62M	100/50	18.3	18	151	22	27	199		97	10.1	6.7
ZN	36M	130/60	18.0	3.9	77	38	14	146		98	11.6	9.2
MMN	55M	140/80	19.0	3.2	95	38	17	167	122		12.1	6.5
PK	57M	110/70	14.8	11	111	40	26	134			15	7.3
SN	30M	140/80	18.0	12	84	42	22	79		101	15.8	
BL	60M	180/100	18.0	24	268	40	19	136		101	11.5	7.1
DZ	31M	130/80	18.0	1.7	106	35	38	984		90	13.2	8.8
SN	39M	120/70	18.0	2.7	85	35	15	124	44	99	13.8	6.0
MM	44F	120/80	16.0	7.3	87	34	27	37	31	91	12.0	14.2
MG	52M	110/80	22	40	296	48	21	31	25	109	15.7	8.7
NN	32M	110/80	19.5	3.4	83	32	6	106			13.2	4.6
TN	38M	120/70	17	2.9	9.7	33	39	46	91	93	11.7	6.7

Table 2: Cardiometabolic and laboratory parameters in Wernicke's encephalopathy

These twenty five subjects had a wide pulse pressure. Ten subjects had evidence of a metabolic acidosis as seen in the serum bicarbonate levels <16 mmol/l. Most subjects had elevated gamma glutamyl transferase levels (normal 6-38 μ/l) in keeping with an alcoholic etiology for their thiamine deficiency.

Readmission Patterns

Most of the 175 patients who responded dramatically to thiamine had single admissions during the period of study. There were seventeen re-admissions noted in nine patients and interestingly, the clinical presentation during these admissions varied from a hyperdynamic circulation to a state of circulatory shock with/without severe metabolic acidosis (Table 3). Case I who initially had pyramidal symptoms, developed bilateral sixth nerve palsy when he represented to hospital four months later and in the third admission a year later he had progression in his deficit with added ataxia and hallucinations. Case II, who had symptoms of nystagmus, blurred vision with headache and a wide pulse pressure on the first admission, was readmitted 15 months later with beriberi heart failure with nystagmus, bilateral sixth nerve palsy and ataxia. The remaining seven patients presented on the first admission with beriberi heart failure: four had coexisting neurologic deficit and two presented with metabolic acidosis and circulatory shock (Table 3). A further two subjects developed cardiovascular collapse combined with metabolic acidosis in subsequent admissions. It is not clear what factors contributed to the change in the subsequent clinical presentation in these patients, but in seven cases with repeated admissions there appeared to be a progression in the cardiac and neurological deficits with each admission, suggesting an increasing thiamine deficiency state that resulted in a worsening neurological and/or metabolic deficit.

No.	Age	Admission 1	Admission 2 (<6months)	Admission 3 (1-2yr)	Admission 4 (>2yr)
1.PM	35M	Pyramidal signs	At 4 mth: Pyramidal signs, Bilateral VI nerve palsy	Pyramidal signs, Bilateral VI palsy, Nystagmus, Gait Ataxia Hallucinations	
2.SS	39M	Vomiting, blurred vision, Nystagmus, PN, headache, BP 125/75		At 15 mth: Vomiting, blurred vision, Nystagmus Bilateral VI palsy Gait ataxia BP 120/70, Gallop.	

3.BM	35M	HF: beriberi BP 140/30	6 mth: vomiting, tremor, nystagmus	18 mth: Vomiting, diplopia, Bilateral VI palsy, Dysmetria	At 2 yrs: Vomiting, diplopia, bilateral ptosis, opthalmoplegia Metabolic acidosis
4.PM	26M	HF: beriberi bilateral ptosis 130/80	Vertigo, Bilateral ptosis, Nystagmus, PN, Gait Ataxia.		
5.ST	36M	HF: beriberi, BP 115/75, Bilateral VI palsy		12 mth: HF Oedema, Dyspnoea BP 140/65, burning legs	
6.CS	43M	HF: beriberi, BP 171/65, Tremor, slurred speech, Gait ataxia, PN		18 mth: HF: Gallop, BP 120/30, Bilateral VI palsy, Nystagmus, PN, Convulsions and Metabolic acidosis.	
7.BM	29M	HF: beriberi BP 150/60, Nystagmus, Bilateral VI palsy, Gait ataxia, PN .	At 1 month: Peripheral Neuropathy		
8.GD	60F	Shock, BP 80/0, Metabolic acidosis: HCO_{3-} 5.7mmol/L		At 1 yr: WE	
9.MM	76M	HF: beriberi Metabolic acidosis: BE –27mmol/l, Lactate22.9mmol/l			At 4 yr: Ataxia, nystagmus BP 120/70

Table 3: Patterns of thiamine deficiency during readmissions

It was also not unusual for the presentation to vary from a neurologic deficit to superimposed cardiac failure in subsequent admissions (Case 2), or from classical hyperdynamic high output state to "Shoshin" type of beriberi in subsequent admissions to hospital. Case 4 who was first admitted in heart failure had three subsequent admissions with worsening neurologic deficit but without heart failure. His fourth admission was characterized by Wernicke's encephalopathy and metabolic acidosis. The remaining six patients had a second admission with worsening neurologic deficit.

Discussion

This review of thiamine deficiency states over a seven year period clearly shows cardiac and neurologic manifestations of thiamine deficiency not infrequently do coexist and manifest with varying patterns of presentation. Combined manifestations of beriberi heart disease and Wernicke's encephalopathy are therefore not rare as previously felt and were present in 10% (18/175) of subjects presenting with thiamine deficiency states in this study. Indeed, cardiovascular manifestations of a high output state identified from the blood pressure readings were frequent and usually unrecognized by the clinician and if these missed signs are added then the prevalence of coexisting neurocirculatory manifestations rises to 25%.

In early studies of clinical and autopsied cases of Wernicke's encephalopathy the heart and the circulatory system have not been the focus of attention [5,6]. Early reports describe signs of cardiovascular dysfunction such as postural hypotension with dizziness, tachycardia and electrocardiographic changes as frequent findings [4], Dyspnoea and sudden unexplained death, however, were clearly indicative of severe cardiovascular instability.

For many years it has been thought that the cardiac and neurological manifestations of thiamine deficiency seldom coexist. The earliest report of circulatory changes in WE described tachycardia, elevated cardiac output and low peripheral resistance in these patients, findings that are consistent with associated beriberi heart disease [8], Gravallese described postural hypotension in seven out of twelve patients with WE, which he attributed to immobility. He reported abnormal tilt tests with postural hypertension and 'systolic overshoot' post-tilt in these patients [8], Earlier reports describe significant autonomic dysfunction with postural hypotension as a consistent feature [11,12].

As mentioned above, in postmortem studies of patients with Wernicke's encephalopathy the heart has not been fully examined. One of the earliest reports of heart involvement was made by Wolf and Levin (1960) who described the autopsy findings of acute Wernicke's encephalopathy in a patient who presented with acute pernicious (shoshin) beriberi. The heart showed hypertrophy and dilatation of the ventricles; the most striking features were hydropic change in most of the cardiac muscle cells, characteristic of beriberi heart disease. In Victor's [5] monograph on WE pulmonary oedema occurred in 5 out of 81 autopsied cases; since tachycardia and dyspnoea were prominent features Victor also cautioned against physical exertion to avoid cardiovascular collapse and death. However, more recently, in Harper's autopsy [10] series of 131 cases, alcoholic cardiomyopathy was documented in only 4%.

In Wernicke's encephalopathy the characteristic lesions are capillary proliferation and haemorrhages in the intermediary bodies, the walls of the 3rd ventricles and the periaqueductal region with extension to the floor of the fourth ventricles resulting in hypotension and hypothermia added to the neurological deficit. The concurrence of tachycardia, elevated cardiac output, low peripheral resistance and postural hypertension led Gravellese and Victor to conclude that all the changes could be explained on the basis of peripheral vasodilation. Postural hypotension has been reported in another series in 71% of patients [12]. A retrospective analysis of WE at our hospital [13], revealed only one case of significant postural hypotension, but seven of the 36 cases reported (20%) in that series had clinical evidence of cardiovascular beriberi. This prompted the author to review the clinical records of all patients admitted with thiamine deficiency to ascertain the prevalence of coexisting manifestations of neurologic and cardiac manifestations. Clearly the coexistence of the two conditions is

not mutually exclusive, and not an uncommon finding if a careful physical examination is performed and the laboratory results evaluated.

To date a clear explanation for the not infrequent coexistence of beriberi heart disease and Wernicke's encephalopathy has not been forthcoming. In early studies Keefer [8] stressed the role of physical effort in precipitating shoshin beriberi and therefore felt that the presence of peripheral neuropathy protected against the development of acute cardiovascular collapse. Peripheral neuropathy is also a common finding in WE and this explanation may explain the uncommon coexistence of the combination of beriberi heart disease and WE. It is however, noteworthy that at our institution we have previously documented peripheral neuropathy in 45% of subjects presenting with cardiac beriberi [7]. Clearly, the peripheral neuropathy did not prevent heart failure from developing, but it was seldom so severe as to be paralytic [7] and in our cases probably occurred on the basis of chronic alcoholism since the neuropathy persisted after treatment with thiamine. At one time it was felt that WE were rare in association with in beriberi heart disease because a more severe depletion of thiamine is required to produce WE. An interesting observation from our current findings is that it was the most severe thiamine deficiency state ie shoshin with metabolic acidosis, that was accompanied by neurological signs of WE [7].

Several clinical implications emerge from this retrospective analysis

Regardless of the predominant mode of presentation, the combination of cardiac and neurological signs should raise the suspicion of a thiamine deficiency state and prompt immediate treatment with thiamine.

Treatment is rewarding and immediately confirmatory of the clinical diagnosis.

The opthalmoplegia resolves within minutes to a few hours. In patients with metabolic acidosis who are in extremis cardiovascular stability is restored almost immediately within minutes to an hour with complete resolution of the metabolic acidosis in 6-8 hours [7].

This study calls for an increasing awareness of thiamine deficiency states amongst emergency physicians. Shoshin beriberi is increasingly being recognised in the intensive care situation and will likely become more manifest in chronic alcoholics and immunocompromised subjects with severe undernutrition [15].

Delay in instituting treatment while investigations such as computerized tomographic scans are being performed and awaiting the results thiamine assays may lead to significant morbidity and may indeed be fatal in shock with severe metabolic acidosis [16,17].

Conclusion

Physical signs of a hyperdynamic state are not specific to cardiac beriberi; tachycardia, bouncing pulse, loud heart sounds and systolic murmurs are frequent in febrile states, anaemia, pregnancy and in thyrotoxicosis. Coexistent cardiovascular manifestations in patients presenting with acute onset of neurological deficit should raise suspicion of a thiamine deficient state. This series of patients with thiamine deficiency states suggests that combined neurocirculatory manifestations of thiamine deficiency are not infrequent and may be a helpful diagnostic pointer to thiamine deficiency. This should prompt immediate institution of thiamine therapy, early in the course of admission. It may avoid the need for CT scans in patients who respond dramatically, and indeed may be lifesaving in subjects with severe metabolic acidosis and circulatory shock.

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