Review Article

Preventing Wernicke's encephalopathy in anorexia nervosa: A systematic review

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Anorexia nervosa (AN) is a common eating disorder that affects 2.9 million people worldwide. Not eating a balanced diet or fasting can cause neurological complications after severe vitamin B1 malnourishment, although the precise signs and symptoms of Wernicke's encephalopathy (WE) are not clear. Our aim was to review the signs and symptoms of WE in patients with AN. We searched MEDLINE, EMBASE, Scopus, and PiCarta on all case descriptions of WE following AN. All case descriptions of WE in AN, irrespective of language, were included. Twelve WE cases were reviewed, suggesting that WE following AN is still a relatively rare neuropsychiatric disorder. WE is characterized by a triad of: mental status change, ocular signs, and ataxia. In alcoholism, this triad is present in 16% of cases, but eight out of 12 AN cases presented themselves with a full triad of symptomatology. Importantly, patients often had a more complex triad than has been previously described, involving vertigo, diplopia, and the consequences of refeeding syndrome. The development of a full triad and additional symptomatology suggests a late recognition of signs and symptoms of WE in AN. A complicating factor is the overlap between symptoms of thiamine deficiency and the symptoms of WE. Specifically, patients who show rapid weight loss are vulnerable for the development of WE. Eating disorders, such as AN, can lead to WE. Prophylactic thiamine checks and treatment in patients with AN are relevant, and in case of suspicion of WE, adequate parenteral thiamine supplementation is necessary.

Key words: anorexia nervosa, clinical nutrition, dietary, thiamine, Wernicke's encephalopathy.

ANOREXIA NERVOSA (AN) IS a serious psychiatric disorder characterized by the inability to maintain an adequate bodyweight, and is recognized as a significant cause of mortality and morbidity.[1] The lifetime prevalence of AN has been estimated between 0.3 and 1.2%.[2,3] Patients suffering from AN have a disturbed conscious and unconscious mental representation of their body,[4] leading to a strong tendency for severe food restriction and purging behavior.[5]

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An adverse consequence of starvation is severe malnutrition. Converging evidence suggests that prolonged food restriction and extreme weight loss occurring in AN are associated with global cerebral atrophy and concomitant cognitive deficits.[6,7] Especially vitamin B1 (thiamine) deficiency has been associated with neuropsychiatric problems, such as depression, emotional lability, cognitive deficits, and a loss of appetite.[8] Thiamine deficiency occurs in 38% of individuals with AN, and is often unrecognized.[9] Recently, selective brain volume alterations of the mammillary bodies have been linked to acute weight changes,[10] reflecting a specific sensitivity to vitamin B1 deficiency of this brain area. Because of the high oxidative metabolism, it has earlier been suggested that the thalamic region,

including the mammillary bodies, is particularly sensitive to thiamine deficiency[11] A possible side-effect of prolonged vitamin B1 deficiency is Wernicke's encephalopathy (WE).

Although the most common cause of WE is vitamin B1 deficiency after severe alcoholism, other causes have also been described in the literature.[12] As descriptions in the literature have not yet been reviewed in detail, the aim of this paper is to review the clinical characteristics of WE in AN, in order to raise the clinician's index of suspicion about this neuropsychiatric diagnosis.

METHODS

We conducted a systematic review of the literature according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement.[13] A comprehensive literature search was performed in MEDLINE, EMBASE, PiCarta, and Scopus using 'Anorexia nervosa' AND 'Wernicke encephalopathy' as search criteria. The last search was carried out on 20 June 2018. There were no language restrictions. All studies with a diagnosis of WE following AN were included, based on Caine's operational criteria for WE.[14] We reviewed the titles and abstracts of these articles, and indexed the data for year of publication, age, sex, body mass index (BMI), symptomatology, comorbid diagnosis, and radiographic findings. All included studies were case reports. Cases were excluded if too little information was available to confirm a diagnosis of WE or no clinical characteristics regarding the patient or course of illness were available.

RESULTS

General overview

We identified 12 case descriptions in the published literature[15–26] (see Fig. 1 for a flow-chart and Table 1 for descriptions), suggesting that AN following WE is a relatively uncommon medical condition in AN. All cases except one were published in the last 15 years, while AN incidence rates remained relatively stable.[2] This highlights the growing awareness of the possible comorbidity of AN. In total, 10 female and two male patients developed WE in AN and presented themselves with WE in the hospital. The average age in case descriptions was 27.8 years (SD = 13.2), with a range of 13–49 years, suggesting that both young and older patients with

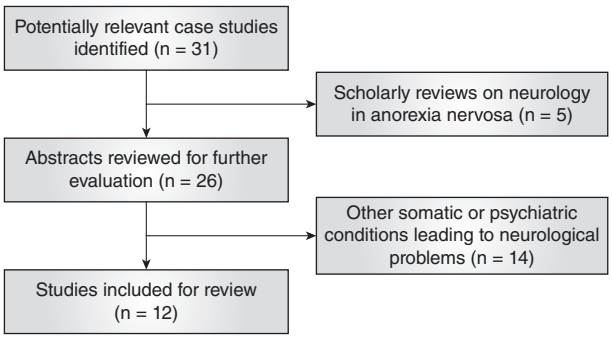

Figure 1. Flow chart of case study inclusion. Illustration of the number of articles identified in literature search and reasons for exclusion. Twelve studies met the inclusion and exclusion criteria.

AN could be at risk for WE. Total weight loss prior to the development of WE was high, with a range between 6 kg in 2 months to 60 kg within 5 months, suggesting a direct link between the development of WE and acute weight loss in WE.

BMI was reported (kg/m^2) for only six patients. Based on the South London and Maudsley Eating Disorder Clinic Guidelines,[27,28] all of these six patients had AN. Two fell in the severe AN category (BMI = 13.5–15), often resulting in a critical reduction of organ functioning and metabolism. One patient had critical AN (BMI = 12–13.5). BMI scores below 12 are directly life-threatening, and scores between 12 and 13.5 often lead to irreversible organ failure.

Signs and symptoms

WE is characterized by the classic triad of ocular motility abnormalities, ataxia affecting primarily the gait, and mental confusion.[12,28,29] A full triad was present in eight cases. This relative occurrence of WE cases presenting with a full triad following AN seems to be higher than that seen earlier in alcoholics with WE (16%)[30] or in patients who developed WE after bariatric surgery (54.2%).[31] We elaborate on the implications of this finding in our discussion. Ocular signs were described as a presenting characteristic of WE following alcoholism in 29% of the patients. Here, 10 out of 12 cases were reported to show ocular signs. Importantly, half of all patients (six patients) also had vertical oculomotor abnormalities, such as upbeat or downbeat nystagmus, or upward gaze palsy. Earlier descriptions of ocular signs in WE found vertical eye movement to

Table 1. Demographic and clinical characteristics

Reference	Sex	Age (years)	Lost weight/ time	BMI	Pre-existent comorbidity	Ataxia	Eye-movement disorder	Mental status change	Additional symptoms	MRI/CT/ EEG
Handler and Perkin[15]	F	25	20 kg/ Months	NA	Agoraphobia, substance abuse, depression	+	+, Downbeat and horizontal nystagmus, diplopia	+, Memory problems	Dysarthria	CT –
Sharma *et al.*[16]	F	49	25 kg/10 weeks	NA	Depression	+	+, Upbeat nystagmus	+, Apathy, Depression		MRI –
Peters *et al.*[17]	F	15	30 kg/6 months	15.6	Seasonal allergies, hypoglycemia	+	+, Vertical and horizontal nystagmus	+, Confusion, bradyphrenia, crying spells	Cranial VI palsy	MRI +
Yang Cho *et al.*[18]	F	35	NA	NA	Febrile sensations, headache	+	+ Ophthalmoplegia, diplopia	–	Neuromyelitis	MRI +
Altinyazar *et al.*[19]	F	16	17 kg/ 1.5 years	14	Depression, medication refusal	+	+, Horizontal nystagmus	+, Delusions, hallucinations, disorientation, confabulations	Refeeding syndrome	EEG +
Saad *et al.*[20]	F	45	NA	16.4	Alcohol abuse	+	+, Ophthalmoplegia	+, Confusion		MRI +
Goban *et al.*[21]	M	14	30 kg/8 months	17.4	General anxiety disorder, infectious mononucleosis, asthma, gastroesophageal reflux	+	+, Multidirectional nystagmus	+, Altered state of consciousness	Refeeding syndrome	MRI +
Renthal *et al.*[22]	M	Adolescent	60kg/5 months	NA	General anxiety disorder	+	+, Diplopia	+	High-pitched voice, paresthesia	MRI +
Kayadibi *et al.*[23]	F	20	NA	NA	Headache	–	–	–		MRI +
Mushtaq *et al.*[24]	F	39		15	Amenorrhea	+	+ Upward gaze palsy, ptosis, unreactive pupil	+ Confusion, confabulations, memory problems		MRI +
Brigadeiro *et al.*[25]	F	13	6 kg/2 months	12.2	Bradycardia	–	–	+ Confusion, psychosis, memory impairment	–	NA
Lopez *et al.*[26]	F	35	NA	NA	Alcohol abuse, gastroenteritis	+	+, Horizontal and vertical nystagmus	NA	Flaccid, paresis of legs	MRI +

+, symptom is present; –, symptom is absent; BMI, body mass index in Kg/m^2; CT, computed tomography; F, female; M, male; MRI, magnetic resonance imaging; NA, not available.

be relatively rare compared to horizontal ocular signs.[32,33] It is likely that this overrepresentation of vertical ocular problems reflects a relatively negative outcome of untreated WE.

Also of interest, complex presentations were common in the case descriptions of AN patients who developed WE, presenting itself as diplopia (4/12), unresponsive pupillary response (1/12) due to pathology on the nervus opticus, or an unusually high-pitched voice (1/12). Also, two patients developed refeeding syndrome, complicating WE. Refeeding syndrome represents a group of clinical findings that occur in severely malnourished individuals undergoing nutritional support. Cardiac arrhythmias, multisystem organ dysfunction, neurological complications, and death are the most severe

symptoms observed in refeeding syndrome.[34] Together, these results suggest that WE in AN here often presents itself with more severe neurological problems than commonly seen in WE following alcoholism, such as a combination of vertical and horizontal ocular deficits, complex cranial nerve problems, and refeeding syndrome. This complexity of WE in reviewed cases suggests relatively late recognition of the syndrome, possibly related to the rarity of the disease.

The case studies presented here often had comorbid psychiatric diagnoses, such as depression in 3/12 cases, general anxiety disorder in 2/12 cases, agoraphobia in 1/12 cases, and alcoholism in 2/12 cases. Next to these already existing psychiatric problems complicating AN, mental status problems in WE had a broader spectrum than that often seen in other forms of WE.[11,12] More specifically, in one case, severe apathy was noted as the presenting characteristic, and another case had acute crying spells as a presenting sign. The existence of mental status problems is elaborated on in the Discussion. In two cases, psychotic symptoms were reportedly severe, despite unaltered consciousness. Usually deliriums with altered states of consciousness are common in WE,[35] although mental status change without altered consciousness has been reported in some cases,[36] and some evidence suggests that a younger age can specifically protect against alterations in consciousness.[31] It is therefore relevant to review a broad range of mental status problems as a possible symptom of WE in AN.

Imaging

Magnetic resonance imaging (MRI) was carried out in nine of the 12 cases and in eight of these nine, MRI revealed radiological alterations in the thalamic area of the brain. This frequency is much higher than the reported sensitivity of 53% in an earlier study on WE in alcoholics,[30] or the 65.6% in an earlier review on bariatric procedures,[30] suggesting that WE occurring because of AN presents a more severe phenotype than after alcoholism or bariatric procedures.

DISCUSSION

AN is an eating disorder characterized by intense fear of gaining weight and the refusal to maintain a bodyweight of at least 85% of the average population weight.[37] AN has the highest mortality rate of any mental disorder, with a general estimate of 5.9%.[38] Rapidly losing weight and malnutrition can cause severe somatic complications, such as WE.[31] The present review has highlighted the signs and symptoms of WE in AN to increase the clinician's suspicion for this neuropsychiatric condition, and to recommend treatment options. The results reviewed here show that WE following AN is a relatively rare condition that presents itself with the classic triad of ataxia, ocular signs, and mental status change in eight of the 12 reviewed cases. A wide range of symptoms in addition to the classic triad is often seen as well, such as diplopia, unresponsive pupils, speaking with a high-pitched voice, general paresis, and refeeding syndrome. Both the extent and severity of the neuropsychiatric symptoms are more intense in WE cases following AN than those described in alcoholics.[12] WE frequently developed after rapid weight loss in already at-risk individuals with AN. Importantly, WE could have been fully prevented by supplying prophylactic thiamine given parenterally. Suboptimal thiamine levels can lead to depressive symptoms, emotional lability, a loss of appetite, and cognitive problems.[8] It is problematic that AN itself has symptomatology overlapping with the results of thiamine deficiency, leading to possible under recognition of thiamine deficiency and adverse neurological consequences. A combination of a psychiatric fear of gaining weight, in combination with a loss of appetite can even lead to a detrimental loss of nutrition in at-risk individuals. Importantly, thiamine is specifically required for glucose metabolism in the brain. Since patients with AN do not consume large amounts of food, their metabolism is relatively reduced, initially preventing them from the development of WE.[9] After a relatively minor change in this fragile but stable situation, due to actively losing more weight or suddenly eating more, WE is more likely to develop, as can be seen in the reviewed case descriptions.

Excessive loss of weight in already existing AN was striking in almost all WE cases reviewed here. In many cases, weight loss was initiated by psychological distress along with pre-existent AN. Prompt treatment of the first symptoms suggestive of WE with high doses of parenteral thiamine replacement therapy is necessary to prevent additional symptoms in WE.[39,40] According to the European Federation of Neurological Societies and the Royal College of Physicians, parenteral thiamine should be given 500 mg

three times daily until symptoms of acute WE resolve.[41] Interestingly, guidelines for treating WE suggest that patients suspected of WE should already be treated as such, and prophylaxis of WE following early signs and symptoms is only achieved by administering parenteral vitamin supplements as oral supplements are not absorbed in significant amounts.[15] Therefore, in AN it is always relevant to give prophylactic vitamin therapy, according to international guidelines, to prevent patients from WE or thiamine-deficiency in general.

Interestingly, the number of case reports on WE in AN seems to have risen in recent decades. It is unclear what critical factor has influenced this rise, although it could be that this is an indirect effect of the rise of eating disorders around the world contributing to more descriptions of WE in AN.[16] Moreover, it could also be that the recognition of WE is currently better than it was two decades ago, as in the past many cases with WE were missed and therefore not actively treated.[15]

In conclusion, AN has the highest mortality rate of any mental disorder. Malnourishment-related WE is a rare but severe and preventable consequence of AN, following starvation and extreme weight loss. This neuropsychiatric consequence specifically warrants attention because of its rapid onset and detrimental course. WE can be fully prevented by supplying prophylactic thiamine given parenterally in patients with AN. The symptomatology of AN and comorbid disorders overlaps with WE, frequently leading to a failure to recognize an altered mental state, oculomotor abnormalities, and ataxia as signs and symptoms of WE. The neurological presentation of WE is probably therefore more severe than that in alcoholics. After onset of symptoms, rapid treatment with high doses of thiamine is still a life-saving measure, directly influencing the core symptoms of WE.

DISCLOSURE STATEMENT

There are no conflicts of interest for any of the authors.

AUTHOR CONTRIBUTIONS

E.O. designed the study and acquired the data, which all authors analyzed. E.O., J.W., M.O., M.v.D., and A.P. wrote the article and revised it. All authors contributed to and have approved the final manuscript.

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