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REVIEW ARTICLE

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Wernicke Encephalopathy in schizophrenia: a systematic review

Erik Oudman[a,b], Jan W. Wijnia[a,b], Misha J. Oey[a,b], Mirjam J. van Dam[a,b] and Albert Postma[a,b]

[a]Experimental Psychology, Helmholtz Institute, Utrecht University, Utrecht, The Netherlands; [b]Korsakoff Center Slingedael, Lelie Care Group, Rotterdam, The Netherlands

ABSTRACT

Introduction: In schizophrenia, patients can experience delusions or hallucinations regarding their food or health status, leading to diminished intake. Fasting or not eating a balanced diet can cause neurological complications after severe vitamin B1 malnourishment. The precise signs and symptoms of Wernicke's Encephalopathy (WE) in schizophrenia are not clear. Our aim, therefore, was to conduct a systematic review of the characteristics of WE in patients with schizophrenia.

Methods: We conducted our search from inception using Mesh terms schizophrenia, Wernicke Encephalopathy, Korsakoff's syndrome. We searched Pubmed, ISI Web of Science, and Scopus. We defined WE as mental, oculomotor, and motoric alterations and thiamine deficiency; schizophrenia was defined as psychosis, hallucinations and/or delusions; adequate WE treatment as >500 mg/day intramuscular or intravenous. Our search yielded 15 WE cases.

Results: WE is characterised by a triad of mental status change, ocular signs and ataxia. In alcohol use disorder, this triad is present in 16% of the cases, but 12 out of the 15 published schizophrenia cases presented themselves with a full triad. Importantly, as an additional characteristic, patients often lost weight within a short period of time.

Conclusions: The development of a full triad and additional symptomatology suggests a late recognition of signs and symptoms of WE in schizophrenia. Prophylactic thiamine checks and treatment in patients with schizophrenia are relevant, and if WE is suspected adequate parenteral thiamine supplementation is necessary.

KEY POINTS

- Only few cases of schizophrenia-related WE have been published in the literature, though challenges in diagnosing and recognising WE suggest that the vast majority of cases go undetected.
- Acute thiamine deficiency leads to Wernicke's Encephalopathy.
- Patients diagnosed with schizophrenia are at risk to develop Wernicke's Encephalopathy.
- Timely treatment with high doses of thiamine can adequately treat Wericke's Encephalopathy.

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Clinical nutrition; dietary schizophrenia; Wernicke's Encephalopathy; thiamine

Introduction

Schizophrenia is a serious psychiatric illness characterised by thought disorders, emotional and perceptional disturbances, and behavioural problems. It affects 0.3%–1.0% of the world's population (Pack 2009; van Os and Kapur 2009; Cunningham and Peters 2014). Nutritional problems in schizophrenia are common due to poor self-care, inability to prepare foods, poor diet and an unhealthy lifestyle (Tsai et al. 2011). In the population of schizophrenia patients, 40.3% have been estimated to be at risk for malnourishment (Kim et al. 2019). Importantly, some patients have food-related command hallucinations or delusions further aggravating the diminished intake.

Converging evidence suggests that prolonged food restriction can result in cognitive problems. Especially vitamin B1 (thiamine) deficiency has been associated with neuropsychiatric problems such as depression, emotional lability, cognitive deficits and a loss of appetite (Van den Eynde et al. 2012). A possible side effect of prolonged vitamin B1 deficiency is Wernicke's Encephalopathy (WE) (Sechi and Serra 2007). Some studies point out that patients with schizophrenia have an altered glucose metabolism with an abnormal accumulation of lactic acid, possibly increasing the chance for the development of WE (Henneman et al. 1954). Similarly, in isotopic dilution studies a defect in the metabolism of carbohydrates in schizophrenia has been found (Sacks 1961).

Although the most common cause of WE is vitamin B1 deficiency after severe alcohol use disorder and malnutrition, other causes sharing the nutritional shortcomings have also been described in the literature (Sechi and Serra 2007). As descriptions in the literature have not yet been reviewed in detail, the aim of this paper was to provide a fuller description of the clinical characteristics of WE in schizophrenia, in order to raise the clinician's index of suspicion about this neuropsychiatric diagnosis and inspiring timely steps to prevent it.

Methods

This systematic review was conducted in accordance to the PRISMA guidelines (Moher et al. 2009). No research protocol has

CONTACT Erik Oudman E.oudman@leliezorggroep.nl Korsakoff Center Slingedael, Experimental Psychology, Helmholtz Institute, Utrecht University, Heidelberglaan 1, Utrecht, 3584CS, The Netherlands

been registered, and there was no funding for this project. We performed a systematic review of the literature. We included case reports and case series. All case studies, irrespective of quality, were included in the systematic review. We excluded reports with only group data (since information on the course of illness and symptomatology was often lacking in all group studies), or when data on clinical presentation were not reported.

Wernicke Encephalopathy

Reports were considered for inclusion if at least one of the following methods of diagnosing WE was reported and the findings reported in the case description were consistent with Caine's operational criteria for WE (Caine et al. 1997): Wernicke's classic triad; autopsy evidence of WE; or clinical response to thiamine (Sechi and Serra 2007). The defining signs and symptoms for WE were as follows: dietary deficiencies, oculomotor abnormalities (reported as nystagmus or ophthalmoplegia), cerebellar dysfunction (reported as falling or imbalance) and an altered mental state (reported as delirium, confusion, and problems in alertness, or cognition).

Schizophrenia

Furthermore, reports had to contain one of the following signs and symptoms of schizophrenia in order to be included: problems in reality filtering, psychosis, hallucinations, delusions, disordered thinking, or negative symptoms presenting without a known somatic cause prior to the onset of the symptoms.

Search strategy and study selection

A comprehensive literature search was performed in Pubmed, ISI Web of Science, and Scopus, using 'Wernicke' AND 'schizophrenia' as MESH terms, and included papers from inception. The last search was carried out on 11 December of 2019. Duplicates were removed. There were no language restrictions. The first author reviewed the title and abstracts of the search yield for eligibility, and screened potentially eligible papers in full text to further assess eligibility. We extracted data from eligible papers in full text.

Outcomes

We extracted and indexed the following data: year of publication, male/female, age, weight loss at WE presentation, aetiology of WE, pre-existent comorbidity, WE symptoms and imaging outcome.

Results

General overview

We identified 15 case descriptions in the published literature (see Figure 1 for a flow-chart and Table 1 for descriptions), suggesting that WE is a relatively uncommon medical condition associated with schizophrenia (McGrath et al. 2008). Ten male patients, and five female patients were included. Six cases reported food-related delusions or hallucinations, such as a food poisoning delusion (Doraiswamy et al. 1994; Newman et al. 1998; Felix et al. 2012), imperative hallucinations that instruct patients to stop eating (Tsai et al. 2004), an extreme slimming cure (Hargrave et al. 2015), or the delusion of food stuck in the throat (Harper et al. 1986). Two cases experienced the delusion that they were dying

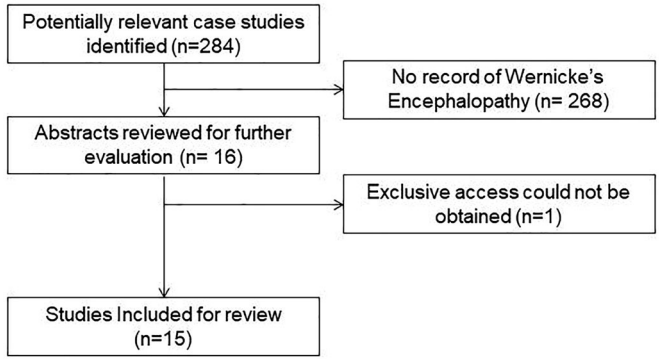

Figure 1. Flow chart of case study inclusion. Illustration of the number of articles identified in literature search and reasons for exclusion. Eleven studies met the inclusion and exclusion criteria.

from a tumour, resulting in diminished intake (Spittle and Parker 1993; Salawu and Kwajaffa 2007). In two cases, vomiting as a consequence of a complication was the origin of the development of WE (Kaineg and Hudgins 2005; McCormick et al. 2011). In one case, there was no apparent reason for the development of WE other than schizophrenia itself (Casanova 1996). In five cases, paranoid schizophrenia was diagnosed (Casanova 1996; Salawu and Kwajaffa 2007; Harrison et al. 2006; Felix et al. 2012; Hargrave et al. 2015). Two cases had schizoaffective disorder (Newman et al. 1998; Kaineg and Hudgins 2005), and in two cases alcohol use disorder was also diagnosed (MacDonell and Wrenn 1991; Park et al. 2009).

The average age in case descriptions was 40.7 years (SD: 9.4 years) with a range between 21 and 61 years, suggesting that both young and older patients with schizophrenia could be at risk for WE. In ten case reports weight loss was reported. Total weight loss prior to the development of WE was high with a range between 0 kilograms and 60 kilograms within five months, suggesting a direct link between the development of WE and acute weight loss in schizophrenia.

Signs and symptoms

WE is characterised by the classic triad of ocular motility abnormalities, ataxia affecting primarily the gait and mental confusion (Caine et al. 1997). A full triad was present in 12 out of 15 cases. Ocular signs have been described as a presenting characteristic of WE following alcohol use disorder in 29% of the patients. In the present review, 12 out of 15 cases showed ocular abnormalities (80%).

Imaging

MRI data were available for 10 of the 15 cases. For all 10 case descriptions, MRI revealed radiological alterations in thalamic area of the brain pathology was visible as atrophy of selective brain structures, including the mamillary bodies and medial thalamic nuclei of the thalamus and ventricular expansion, probably indicative of atrophy of surrounding grey matter nuclei.

Discussion

Schizophrenia is a serious psychiatric illness characterised by thought disorders, emotional and perceptional disturbances, and behavioural disturbance (Van Os and Kapur 2009). Food-related delusions or hallucinations, diminished food intake, or vomiting can cause severe somatic complications in schizophrenia, such as

Table 1. Demographic and clinical characteristics.

Author	Gender	Age	Lost weight/time	Aetiology	Pre-existent comorbidity	Ataxia	Eye-movement disorder	Mental status change	MRI/CT/EEG/ Autopsy
MacDonell and Wrenn (1991)	M	41		N.A.	Alcoholism and schizophrenia	+	+	+	CT −
Spittle and Parker (1993)	M	61		Delusion – Dying from an ovarian tumour	Schizophrenia with catatonia	+	+, opthalmoplegia	+, no verbal communication	N.A.
Doraiswamy et al. (1994)	F	37	31.8 kg	Delusion – Foods are dangerous	Delusions	+	+, nystagmus and opthalmoplegia	+, Amnesia, apraxia	MRI +
Casanova (1996)	F	36	No weight loss	Delusions – police as perpetrator	Paranoid schizophrenia	−	−	+, lack of insight	Autopsy +
Newman et al. (1998)	M	46	N.A.	Delusion – Food poisoning	Schizoaffective disorder	+	+, rotary nystagmus	+ memory problems, agitation, dysartria	N.A.
Tsai et al. (2004)	M	41	17 kg/1.5 years	Voices asked to stop eating	Schizophrenia	+	+, horizontal nystagmus	+, dysartria, memory loss	MRI +
Kaineg and Hudgins (2005)	F	21	13 kg / 4 months	Vomiting	Schizoaffective disorder	+	+, nystagmus	+, disorientation, slurred speech	MRI +
Harrison et al. (2006)	M	51	18.1 kg/3 months	Stopped eating in paranoia	Paranoid schizophrenia, Seizures	+	+, Opthalmoplegia and nystagmus	+, disorientation, agitation	MRI +
Salawu and Kwajaffa (2007)	M	37	60kg/5 months	Delusion – Dying from a tumour	Paranoid schizophrenia	+	+, opthalmoplegia	+, disoriented, agitated	N.A.
Harrington et al. (2007)	M	Middle aged		Anorexia	Alcoholism and schizophrenia	−	−	+, memory and alertness	MRI +
Park et al. (2009)	F	42	5kg	Vomiting	Schizophrenia, Oesophagus carcinoma, metastasis	+	+, nystagmus	+, memory loss	MRI +
McCormick et al. (2011)	M	Mid30s	11.3 kg/Three months	Soda pop diet, Delusion – food poisoning	Paranoid schizophrenia	+	−	+ Confusion, lack of insight, memory problems	MRI +
Felix et al. (2012)	F	45	N.A.	God delusion	Schizophrenia	+	+, upbeat nystagmus	+ disorientation, confusion	MRI +
Langlois et al. (2014)	M	36	22.7 kg	Slimming cure	Paranoid schizophrenia	+	+, nystagmus	+, amnesia, agnosia	MRI +
Hargrave et al. (2015)	M	35	13.6 kg/ year	Delusional sensation of food stuck in his throat	Pneumonitis Depression Delusions	+	+, nystagmus	+, memory, confused, disoriented	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; N.A.: not available.

Wernicke's Encephalopathy (WE). The present review highlighted the signs and symptoms of WE in schizophrenia to increase the clinician's suspicion for this neuropsychiatric condition, and recommend treatment options.

The results reviewed here show that WE following schizophrenia has seldom been reported in the literature. Importantly, WE is known to be under-recognize, and the vast majority of cases are missed during life. WE presents with the classic triad of ataxia, ocular signs, and mental status change in 12 out of the 15 reviewed schizophrenia cases. WE frequently developed after rapid loss of weight in already at risk individuals with schizophrenia. WE could have been fully prevented by supplying prophylactic thiamine given parenterally. Importantly, thiamine is specifically required for glucose metabolism in the brain. Some studies showed that more thiamine might be needed in schizophrenia because of an altered glucose metabolism in schizophrenia (Henneman et al. 1954; Sacks 1961). In one case study, there was no adverse weight loss leading to WE, suggesting that less efficient processing of glucose could be the cause of thiamine depletion in a relatively normal diet.

In 80% of the reported cases a full triad of WE was present (Kaineg and Hudgins 2005). This finding could be suggestive for a relatively late recognition of suboptimal thiamine levels leading to WE in schizophrenia. Suboptimal thiamine levels can lead to apathy, a loss of appetite, fatigue, irritability and extrapyramidal symptoms (Sechi and Serra 2007). It is problematic that schizophrenia itself has symptomatology overlapping with the results of thiamine deficiency, leading to possible under recognition of thiamine deficiency. Moreover, it is possible that clinicians are not used to think about WE in non-alcoholic schizophrenic patients. Prompt treatment of the first symptoms suggestive of thiamine deficiency with high doses of parenteral thiamine replacement therapy is necessary to prevent progression of WE (Thomson et al. 2002; Isenberg-Grzeda et al. 2012). According to the European Federation of Neurological Societies and the Royal College of Physicians, parenteral thiamine should be given 500 mg, 3 times daily until symptoms of acute WE resolute (Thomson et al. 2002). Because of the possible increased requirement of thiamine in schizophrenia, it is relevant to check the vitamin status in schizophrenia patients who lose weight, and start prophylactic vitamin therapy.

A limitation of this systematic review is the relatively small number of case reports reviewed here. It is likely that some cases on WE are not reported in the literature, and it is unknown whether those cases show other characteristics as the ones reviewed here. Admittedly a more substantial sample of cases would strengthen the substantiation of this manuscript. Nevetheless we want to emphasise here that the high amount of malnutrition in general in schizophrenia (40%) gives reason for sincere caution to be taken by treating physicians and psychiatrists.

In conclusion, diminished food intake or vomiting in schizophrenia can result in malnourishment-related WE. The neuropsychiatric consequence of malnourishment warrants attention because of its rapid onset and detrimental course. Symptoms of malnourishment can be confused with the negative symptoms of schizophrenia (lack of interest, apathy, and tiredness). WE in schizophrenia can be fully prevented by supplying prophylactic thiamine given parenterally to patients at risk for weight loss. After onset of symptoms, rapid treatment with high doses of thiamine is a life-saving measure, directly influencing the core symptoms of WE.

Author contributions

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

Disclosure statement

No potential conflict of interest was reported by the author(s).

ORCID

Erik Oudman http://orcid.org/0000-0002-4441-0365
Mirjam J. van Dam http://orcid.org/0000-0002-5427-6454

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