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Hallucinations and Vitamin B_{12} Deficiency: A Systematic Review

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Keywords
Cobalamin · Multimodal hallucination · Nitrous oxide · Pernicious anaemia · Vegetarianism

Abstract

Introduction: Vitamin B_{12} deficiency is primarily associated with pernicious anaemia, polyneuropathy, and spinal-cord disease, but publications on its association with hallucinations are on the rise. ***Methods:*** I carried out a systematic literature search on these hallucinations in PubMed, PsycINFO, and Google Scholar, up until July 1, 2023. ***Results:*** The search yielded 50 case studies published between 1960 and 2023. The hallucinations described therein are predominantly visual and/or auditory in nature, with 20% being specified as complex, compound, or panoramic. They are often described in the context of vitamin B_{12}-related neuropsychiatric conditions such as dementia, delirium, epilepsy, psychotic disorder, schizoaffective disorder, bipolar disorder, depressive disorder, catatonia, or obsessive-compulsive disorder. In the context of such disorders, they tend to appear first and also often appear to be the first to disappear with cobalamin treatment. Within an average of 2 months, full amelioration was thus obtained in 75% of the cases and partial amelioration in the remaining 25%. Remarkably, a quarter of the cases involved therapy-resistant hallucinations that fully resolved under cobalamin monotherapy, while other neuropsychiatric manifestations of vitamin B_{12} deficiency disappeared in 60% of the treated cases. Only 32% of the cases involved comorbid pernicious anaemia. This suggests that two separate or diverging pathways exist for perceptual and haematological symptoms of vitamin B_{12} deficiency. ***Conclusion:*** In the light of the high prevalence rate of vitamin B_{12} deficiency in the general population, the findings here presented should be interpreted with great caution. Nonetheless, they offer cues for further research and experimental application in clinical practice. This may be especially relevant in light of the recent increase in the popularity of vegetarianism and the recreational use of nitrous oxide (laughing gas), which are both risk factors for vitamin B_{12} deficiency.

Plain Language Summary

It has been known for a long time that low levels of vitamin B_{12} may cause pernicious anaemia and diseases of the nervous system. I here provide a systematic review on a less well-known association, namely with hallucinations. My search yielded 50 case studies published between 1960 and 2023. The hallucinations described therein are predominantly visual or auditory in nature. They tended to appear before any other vitamin-B_{12}-related disorders, and they also appeared to be the first to go away when treatment was started with vitamin

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B_{12}. Within an average of 2 months, the hallucinations thus treated vanished completely in 75% of the cases and partly in the remaining 25%. Remarkably, a quarter of the cases involved hallucinations that had shown to be resistant to treatment with antipsychotics and sometimes even to electroconvulsive therapy (ECT). Nonetheless, they fully resolved under treatment with vitamin B_{12} alone, while other symptoms disappeared in 60% of the treated cases. Another remarkable finding was that only 32% of the people described showed signs of pernicious anaemia. Since low levels of vitamin B_{12} are very common in the general population, the findings here presented should be interpreted with great caution. Nonetheless, they offer cues for further research and experimental treatment. This may be especially relevant in light of the recent increase in the popularity of vegetarianism and the recreational use of laughing gas, which may both cause levels of vitamin B_{12} to decline.

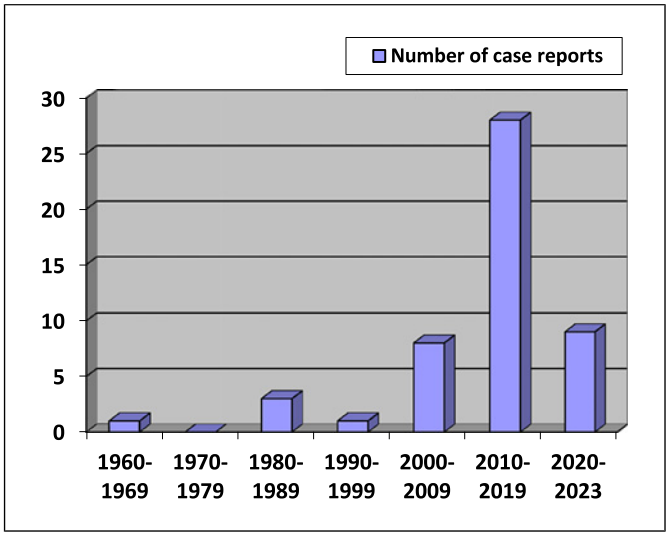

Fig. 1. Number of published case reports on vitamin B_{12}-related hallucinations per decennium (N = 50).

Introduction

In a society where vegetarianism is on the rise and the recreational use of laughing gas has become disturbingly common, the need to prevent health problems due to vitamin B_{12} deficiency is more urgent than ever [1, 2]. In this context, an underexposed issue is the risk of hallucinations. Although reported on since the 1960s, vitamin B_{12}-related hallucinations did not become a topic of somewhat wider interest since the start of the 21st century (Fig. 1). Since these hallucinations are rarely the sole manifestation of this vitamin deficiency, clinical reports often describe them in the wider context of vitamin-B_{12}-related neuropsychiatric conditions such as dementia, delirium, epilepsy, psychotic disorder, schizoaffective disorder, bipolar disorder, depressive disorder, catatonia, or obsessive-compulsive disorder [3–6]. In 2021, Nichols et al. [7] published a case report on vitamin-B_{12}-related hallucinations that was accompanied by an overview of 17 published cases. The authors concluded that (a) these hallucinations do not always receive the attention they deserve, especially in comparison with other manifestations of vitamin B_{12} deficiency, (b) prompt cobalamin supplementation may lead to complete remission of these hallucinations, and (c) the biological link between hallucinations and vitamin B_{12} deficiency has remained elusive.

Clinical Relevance

With an estimated lifetime prevalence of vitamin B_{12} deficiencies of 2.5–26% in the general population [8, 9] and of 3–40% in the elderly [10], the purported association with hallucinations may well be a matter of coincidence. That said, vitamin B_{12} is so essential to normal brain structure and functioning that it is equally hard to dismiss the possibility that deficiencies do play a role in their mediation, or at least in some types of hallucination. Modest clinical studies, moreover, provide preliminary evidence of a causal relationship. It has been shown, for example, that some hallucinations are amenable to cobalamin therapy and that occasionally, cobalamin supplementation may even be efficacious in people resistant to psychotropic medications [11–14]. In one remarkable case, a 54-year-old woman with vitamin B_{12} deficiency suffering from hallucinations and catatonia, who had remained unresponsive to lorazepam for 3 months, fully recovered on cobalamin [15]. Another remarkable case involves a 35-year-old psychotic and suicidal man who, having shown to be resistant to chlorpromazine and electroconvulsive treatment (ECT), fully recovered on cobalamin monotherapy in 8 days [16]. What makes the latter case even more exceptional is that vitamin B_{12} levels had been within the normal range (436 mg/mL) and that the choice for this unorthodox treatment was inspired by the total gastrectomy that the patient had undergone 9 years before. As this case demonstrates, the question of what should count as a deficiency of vitamin B_{12} is also worth exploring. Yet another reason to focus on the present topic is the finding that these hallucinations may precede better-known symptoms of vitamin B_{12} deficiency, such as pernicious anaemia, polyneuropathy, and spinal cord disease, and may thus serve as early warning signs for these more severe complications [8, 17]. To shed light on

the role of vitamin B_{12} deficiency in the mediation of hallucinations, I will review below all published case reports on this topic and summarize what is known about possible associations and underlying mechanisms.

Methods

I carried out an (unregistered) systematic search in PubMed, PsycINFO, and Google Scholar for papers published up until July 1, 2023 using the search terms *cobalamin* and *vitamin B_{12}* in combination with *hallucination*, *psychosis*, *schizophrenia*, *dementia*, and *delirium*. I complemented the digital searches with backward searches. There were no language restrictions, which is why papers in English, French, Japanese, and Arabic were included. Papers were excluded when they contained no original case descriptions, and when the phenomena reported did not comply with the definition of hallucination (i.e., a percept, experienced while awake, in the absence of a corresponding stimulus in the outside world). For practical reasons, I operationalized vitamin B_{12} deficiency as a serum level below the range of 150–180 pmol/L (=200–250 pg/mL). Since the exact cut-off point between these two minimum levels was different for different hospitals and laboratories, I followed the conventions described in each original paper when deciding what should count as a hypovitaminosis. From all relevant reports, I extracted the following data: (i) year of publication, (ii) sex and age of the patient, (iii) type of hallucination, (iv) clinical diagnosis, (v) test results, (vi) type of treatment, and (vii) outcome. Given the small numbers, I did not perform any statistical tests.

Results

The initial search yielded 22 potentially relevant papers, of which 13 contained original case descriptions. Cross-references yielded another 35 papers. From the total number of 48 articles, I extracted 50 pertinent case descriptions (summarized in the online suppl. material, as shown in Table S1; for all online suppl. material, see https://doi.org/10.1159/00054003; PRISMA flow diagram shown in Fig. 2). Since 48% of the people described were female, the sex ratio was virtually one. With the mean age for women being 36 years (range 13–86 years) and for men 39 years (range 8–75 years), there was no statistically significant difference for age.

Phenomenology

Of the 50 individual case descriptions that I retrieved on hallucinations associated with vitamin B_{12} deficiency, 82% provided a specification of the sensory modalities involved (overview shown in Fig. 3). Visual hallucinations were reported most often (42% of the total group), with 12% being specified as complex (i.e., of a relatively high complexity, as in seeing faces or animals) and 4% as simple (i.e., of a low complexity, such as the seeing of stars or lines), while 26% were unspecified. Auditory hallucinations were almost as prevalent (40%), with 26% being verbal in nature, 2% nonverbal, and 12% unspecified. Three people (6%) reported on compound hallucinations, also with visual and auditory components. Olfactory hallucinations were reported in 4% of the cases, and there were single cases (2% each) of tactile, kinaesthetic, and panoramic hallucinations, the latter – again – with visual and auditory components. In addition, there was a single reference to hallucinations combined with thought echo [18] and another to hallucinations co-occurring with dysmorphopsia, i.e., a visual distortion rather than a hallucination where straight lines are seen as wavy [19]. Paraesthesia was described in 10% of the cases.

Besides the mention of the involvement of the sensory modalities, 40% of the reports provided somewhat richer phenomenological descriptions (shown in Table 1). In 50%, verbal auditory hallucinations were described, half of which were experienced as threatening in nature and a third as comments/commands. Another 50% were described as complex visual hallucinations, half of which involved humans or other entities such as spirits or deceased relatives. Of these, 70% were described as threatening and/or distressing. Although not mentioned explicitly in the original reports, three cases were reminiscent of *jinn* encounters, i.e., dealings with spirits, as described in the Qu'ran, which Allah created out of smokeless fire [23, 27, 34]. Two other cases concerned zoopsia, i.e., featuring animals (bugs and "fast-moving birds"), and another two involved simple visual hallucinations (seeing lights and seeing colours, the latter possibly a case of coloropsia). In sum, the majority of the fuller descriptions concerned visual and/or auditory hallucinations, most of which were described as complex in nature, with most being rated as negative by the percipients.

Other Neuropsychiatric Symptoms

Additional psychiatric symptoms (e.g., paranoia, delusions, catatonia, anxiety, mood changes, agitation, aggression) were mentioned in 84% of all cases. Moreover, 66% of the patients presented with neurological symptoms such as peripheral neuropathy, dysstasia, gait instability, muscle weakness, rigidity, ataxia, fluctuations of consciousness, and memory impairments. In three cases (6%), patients went on to develop paraplegia due to a subacute combined degeneration of the spinal cord [31, 35, 36]. In one case, this was complicated by respiratory failure requiring mechanical ventilation [35].

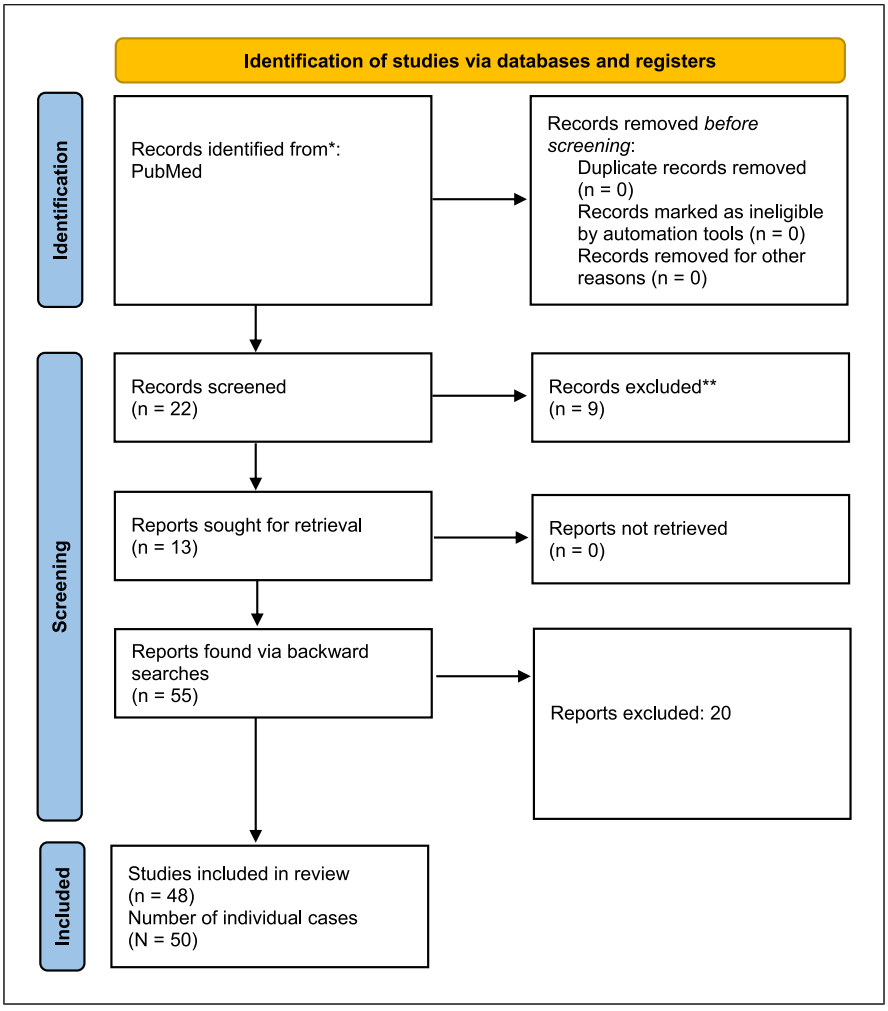

Fig. 2. PRISMA flow diagram.

Clinical Diagnoses and Underlying Disorders

Since several of the 50 patients described in the original reports had received more than one clinical diagnosis, the total number of established neuropsychiatric diagnoses was 63. The most prevalent ones were schizophrenia spectrum disorder (46%, including 2 cases of catatonic psychosis and one of manic psychosis), psychotic depression (11%), epilepsy (11%), delirium (10%), encephalopathy (6%), and dementia (3%). The remaining group comprised single cases of parkinsonism, Charles Bonnet syndrome, cerebral venous thrombosis, leukoencephalopathy, and cases with general descriptive labels such as "neuropsychiatric disorder," "neuropsychiatric complications," "neuropsychiatric manifestations," and "neurological syndrome." In addition, 16 patients (32%) had been diagnosed with pernicious anaemia. The underlying cause or causes of vitamin B_{12} deficiency were mentioned in 82% of the cases, 36% of which comprised malnutrition, 24% malabsorption (in association with atrophic gastritis, partial stomach resection, resection of the terminal ileum, enteritis, or giardiasis), 16% a vegan, vegetarian, or lactovegetarian diet, 14% the abuse of nitrous oxide (N_2O, laughing gas), 12% cobalamin C disease, 4% alcohol abuse, and 2% prolonged treatment with folate.

Treatment and Outcome

All 50 patients had been treated with cobalamin or variants thereof (e.g., hydroxocobalamin, methylcobalamin), mostly intravenously or intramuscularly at first, followed by oral supplementation. Two people were lost to follow-up. Of the remaining 48 patients (96%), 71% were treated exclusively with cobalamin and 29% with cobalamin plus adjuvant medicines such as antipsychotics, antidepressants, benzodiazepines, or antiepileptics. In all, 75% of the patients showed full recovery of their hallucinations, including a subgroup of 60% who also showed full recovery of other vitamin-B_{12}-deficiency-related

symptoms. The remaining 25% showed partial recovery. Of the 48 cases, 23% had previously been resistant to treatment with antipsychotics and/or antidepressants, benzodiazepines, antiepileptics, and sometimes even ECT, but were found to be amenable to cobalamin monotherapy. The mean duration of recovery after the initiation of cobalamin treatment was 57 days (range: 1–365 days). The mean duration of follow-up was 307 days.

Discussion

Summary of the Main Findings

The 50 case reports here reviewed reported on hallucinations in association with vitamin B_{12} deficiency. These mainly involved the visual and auditory modalities, with 20% of them being complex, compound, or panoramic in nature. As has been known for some time, when left untreated such hallucinations may progress into severe neuropsychiatric and neurological disorders with a potentially lethal outcome. Monotherapy or adjuvant treatment with cobalamin proved effective in virtually all cases, leading to full amelioration of the hallucinations in 75% and to partial amelioration in the remaining 25%, all within an average time span of 2 months. The discovery that almost a quarter of the cases involved hallucinations resistant to treatment with antipsychotics (and in some cases even ECT) that fully resolved under cobalamin monotherapy is unparalleled in the pharmacological management of hallucinations and therefore noteworthy in and of itself. The other neuropsychiatric manifestations of vitamin B_{12} deficiency tended to disappear later during the treatment phase, with all symptoms fully disappearing in 60% of the cases. With a mean follow-up of 10 months, these results can be called modest, but robust. Finally, in line with the work of McAlpine [17] and other pioneers in this area, pernicious anaemia and other types of vitamin-B_{12}-related anaemia were found to be relatively rare comorbidities of these hallucinations (being chronicled in 32% of the cases). To provide these results with more contexts, I will touch briefly on some historical aspects and then go on to examine underlying neurobiological mechanisms, epidemiological findings, and finally implications for clinical practice and research.

Historical Aspects

The discovery of vitamin B_{12} would have been unthinkable without the development of the clinical concept of pernicious anaemia during the 19th century. In 1872, the German internist Michael Anton Biermer (1827–1892) provided what has been called the first adequate description of this haematological disorder, which he named "progressive pernicious anaemia" because of its association with rapid decline and fatality [37]. Another key step towards the discovery of vitamin B_{12} was the insight the American haematologists George Minot (1885–1950) and William Murphy (1892–1987) gained in 1926 that this life-threatening type of anaemia could be treated with the aid of liver extracts [38]. The isolation of vitamin B_{12} from liver extracts followed in 1947, in the lab run by Mary Shaw Shorb (1907–1990), Karl Folkers (1906–1997), and Alexander Todd (1907–1997). Together with Dorothy Hodgkin (1910–1994), Todd went on to elucidate the chemical structure of vitamin B_{12} during the mid-1950s, with the first case descriptions of hallucinations in the context of vitamin B_{12} deficiency appearing shortly thereafter [39, 40]. That said, as far back as 1905 Frank Warren Langdon (1852–1933) had already published 2 cases involving auditory hallucinations in conjunction with pernicious anaemia [41]. Even though the causal role of vitamin B_{12} in this type of anaemia had not yet been established at the time, with hindsight Langdon's 1905 paper may well be considered the first one describing this type of hallucination.

Aetiopathology

Aetiologically, the hallucinations under discussion here are attributed to the depletion of the body's natural store of vitamin B_{12} and the brain's subsequent shortage of biologically active vitamin B_{12}. Vitamin B_{12} is a water-soluble nutrient that in humans acts as a cofactor for two basic biochemical pathways. Since these pathways are of vital importance to fundamental processes such as DNA synthesis, the production of red blood cells, and neurological functioning, deficiencies of vitamin B_{12} can cause an array of disorders, ranging from haematological and gastrointestinal to cutaneous, neurological, and psychiatric syndromes [42]. Among these disorders, the best known is pernicious or macrocytic anaemia. Under normal physiological circumstances, our natural store of vitamin B_{12} (amounting to 3–5 mg in adults) is not easily exhausted. However, an intake of less than 2.4 μg per day may lead to depletion within 2–5 years [37]. Since we depend for our vitamin B_{12} on (mainly animal) food, the best-known cause of deficiencies is a reduced intake of meat, fish, and other food rich in this vitamin (for an overview of causes, see [43]). This may derive from dietary habits, malnutrition, fasting, or starvation. Moreover, deficiencies may be caused by malabsorption (as in nonimmune chronic atrophic gastritis, total or even partial gastrectomy, and ileal resection), inherited metabolic diseases (such as cobalamin C disease; see below), the use of certain

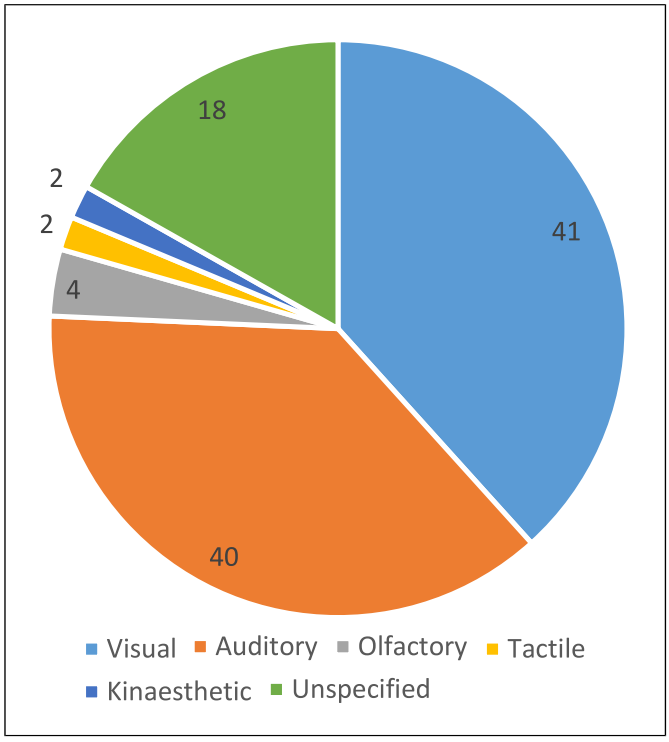

Fig. 3. Distribution of vitamin B_{12}-related hallucinations per sensory modality, in percentages.

medicines (e.g., proton pump inhibitors or metformin), and the use of certain illicit substances (notably nitrous oxide, see below). The way in which deficiencies come to expression depends mainly on genetic and metabolic factors, only some of which are sufficiently understood. Several hypotheses have been put forward to explain why some people develop haematological and others cutaneous, gastrointestinal, or neuropsychiatric conditions, but as yet none of these have been empirically corroborated [44]. Of note, even the severity of vitamin B_{12} deficiency is not a reliable predictor of the ensuing disease phenotype [37].

Nitrous Oxide Use

A timely aspect of the current topic is the association between hallucinations, vitamin B_{12}, and the use of nitrous oxide. After two previous surges in the number of publications on hallucinations in the context of nitrous oxide use – around 1900 and during the 1980s – the past decade has witnessed yet another surge. During the earlier two epochs, publications centred on the alleged capacity of nitrous oxide to evoke sexual hallucinations and on the related issue of whether health professionals might sometimes resort to sexually inappropriate behaviour while selling the sensations off as "sexual hallucinations" [45]. The more recent surge of publications on hallucinations and nitrous oxide has to do with the substance's use as a street drug. As such, it is used in much larger and sometimes escalating quantities by ever increasing numbers of otherwise healthy people [1]. Systematic studies on the types of hallucination its misuse evokes have not been published as yet, and, curiously, this time around reports on sexual hallucinations are virtually lacking. Instead, the focus is on the neurological sequelae of nitrous oxide use and the role of vitamin B_{12} deficiency. Nitrous oxide, a colourless, non-flammable gas, has the capacity to deplete the liver's vitamin B_{12} reserves much faster than malnutrition or dietary habits, provided that it is inhaled frequently and in relatively large quantities. In 2021, Paulus et al. [46] reviewed the role of vitamin B_{12} deficiency in nitrous-oxide-induced psychiatric symptoms. The authors found that of the 31 published cases, 52% involved hallucinations and 48% neurological symptoms, while in 45% of the cases, vitamin B_{12} concentrations had been below the hospitals' reference ranges. Since only three cases with hallucinations fell into the latter group (published previously by [30, 47, 48]), on the basis of this article no firm conclusions can be drawn as to the role of vitamin B_{12} in nitrous-oxide-related hallucinations. Another complicating factor is that nitrous oxide may also be directly responsible for mediating hallucinations by blocking NMDA receptors on gamma-aminobutyric acid interneurons or by activating dopaminergic neurons [49]. Moreover, it is known that nitrous oxide blocks the conversion of homocysteine to methionine, thus increasing homocysteine levels (a known risk factor for psychosis) and decreasing vitamin B_{12} levels [50]. In sum, the capacity of nitrous oxide to mediate hallucinations is well known, even though case descriptions are few and systematic large-scale studies are even fewer.

Cobalamin C Disease

Within the framework of this review, another mechanism worth highlighting is cobalamin C disease. Raveendranathan et al. [51] described a 27-year-old vegetarian woman who heard voices and who had been diagnosed with schizophrenia >10 years before. She had been treated with clozapine, valproic acid, and ECT. Although she had initially improved, she relapsed but then showed a dramatic clinical improvement within 2 days after the initiation of adjuvant treatment with cyanocobalamin. Interestingly, her vitamin B_{12} serum level had been within the normal range (236 pg/mL, N 174–878 pg/mL). One explanation for such cases is that cobalamin C may be deficient [35]. This inborn error of metabolism typically

Table 1. Phenomenological descriptions of hallucinations associated with vitamin B_{12} deficiency (n = 20)

Publication	Description
Evans et al. [20] (1983)	Seeing lights identified as UFOs, and hearing Jesus speak
Heap and Mumford [21] (1989)	Seeing small moving objects "like fast moving birds"
Buchman et al. [22] (1999)	Seeing dead relatives and hearing them speak
Masalha et al. [23] (2001)	Seeing a giant black monster with a horrible face trying to strangle her
Masalha et al. [23] (2001)	Seeing terrifying humans trying to assault her, and hearing threatening remarks
Herr et al. [13] (2002)	Seeing colours and smelling smoke
Rajkumar and Jebaraj [24] (2008)	Hearing multiple female voices
Abi-Abib et al. [25] (2010)	Seeing bugs in the food
Bourgeois et al. [19] (2010)	Seeing male characters walking in a supermarket, as well as scary faces, and visions of her childhood, plus seeing lines distorted
Bar-Shai et al. [26] (2011)	Hearing voices threatening him and accusing him of financial dishonesty
Çim and Değer [27] (2015)	Seeing a woman threatening to kill her
Dhananjaya et al. [18] (2015)	Hearing a running commentary and commands
Hadinezhad et al. [28] (2016)	Seeing his house being on fire, with people being trapped inside whom he saw and heard screaming
Tufan et al. [29] (2018)	Seeing a white, man-like shape, hearing knocking and ringing, smelling burnt rubber, perfumes, and tobacco, especially in the evening
Kim et al. [30] (2019)	Hearing voices giving comments
Silva et al. [14] (2019)	Seeing spirits of dead relatives forbidding her to take medication
Zimba and Saylor [31] (2019)	Hearing voices accusing the examiner of trying to harm him
Kimoto et al. [32] (2020)	Seeing the form of a middle-aged man
Nichols et al. [7] (2021)	Seeing objects
Sood and Parent [33] (2022)	Seeing and hearing people threatening to shoot him and harm his spine

presents with normal or even high serum vitamin B_{12} levels without macrocytic anaemia. It may have an early onset (i.e., in children) or a late onset (in adults). A preliminary diagnosis can be made with the aid of plasma homocysteine levels and can be further confirmed with the aid of fibroblast cultures or genomic amplification and direct sequencing of the coding exons of the MMACHC gene, including the flanking regions [52]. In the present review, I found 6 cases of cobalamin C disease (12% of the cases reviewed) that presented with hallucinations [35, 52–56].

Mediation of Hallucinations

Healton et al. [42] divided the neuropsychiatric sequelae of vitamin B_{12} deficiency into six main categories comprising (i) peripheral neuropathy, (ii) myelopathy, (iii) neuropathy, (iv) optic neuropathy, (v) paraesthesias without abnormal neurological findings, and (vi) altered mental states. Although consciousness tends to be unaltered in vitamin-B_{12}-related neuropsychiatric disorders, in their overview the authors relegated hallucinations to "altered mental states." It is tempting to hold demyelination responsible for the mediation of such hallucinations – or some other structural defect caused by vitamin B_{12} deficiency – but I found no empirical studies to support this. Moreover, a structural hypothesis would be at odds with case descriptions where hallucinations disappeared within days upon cobalamin supplementation. Another as-yet unanswered question is whether vitamin B_{12} deficiency is directly responsible for the mediation of these hallucinations, or, perhaps indirectly, via its effect on other vitamins (e.g., folate) or amino acids

(e.g., homocysteine). After all, both folate deficiency and elevated levels of homocysteine are established risk factors for psychosis. Here, the work of Allott et al. [57] is worth mentioning, who supplemented vitamin B_{12}, vitamin B_6, and folic acid in 100 patients with a first psychosis. Although the authors only noted a modest effect, they were motivated by the notion that the compounds used are homocysteine-reducing agents.

Regarding the brain networks activated in vitamin B_{12}-related hallucinations, the findings from this review indicate that it is the visual and auditory networks that are most often involved. Moreover, the complex, compound, and panoramic hallucinations described in 20% of the cases suggest the involvement of higher-order integrative centres and a mechanism akin to perceptual release. This is a mechanism where endogenous percepts are believed to be released from phylogenetically "older" and anatomically "lower" parts of the brain, and "projected outward." The metaphor used by West [58] is that of a person looking out the window, with a fire crackling in the fireplace behind them while outside it is gradually getting darker. At some point, the scenery outside will no longer be visible and make place for the fire inside being reflected in the window. The perceptual release hypothesis likewise attributes hallucinations to a loss of awareness of one's actual surroundings where regular sense perceptions are replaced by hallucinated images. However, as noted, such "release" hallucinations comprised a minority of the cases reviewed. Moreover, it is as yet unclear whether the cases reported on truly represent the most prevalent types of hallucination in vitamin B_{12} deficiency. Since even in psychiatry it is rare to assess whether hallucinations are experienced in all sensory modalities [59, 60], we may ask ourselves whether hallucinations in other sensory modalities may have been missed in the studies reviewed and, in consequence, whether additional perceptual networks and mechanisms may perhaps also be involved.

Prevalence

Given the scarcity of published research, the prevalence of hallucinations associated with vitamin B_{12} deficiency is unknown. Testing 100 vegetarians and 100 non-vegetarians in the general population, Kapoor et al. [61] found that the vegetarians had significantly lower mean levels of vitamin B_{12} (238 vs. 401 pg/mL) and a substantially greater number of neuropsychiatric symptoms. Frequencies for depression were 31% versus 12% and for psychosis 11% versus 3%. Unfortunately, the authors did not inquire into the presence of hallucinations per se. All other prevalence studies were carried out in clinical populations. During the 1950s, Holmes studied 25 clinical patients with vitamin B_{12} deficiency, 14 of whom showed cerebral manifestations, including three (12%) who reported visual or auditory hallucinations [39]. In another clinical study, Jayaram et al. [5] collected 19 cases of vitamin B_{12} deficiency with psychiatric manifestations and found that "the majority" experienced verbal auditory hallucinations. A study among 369 patients with low vitamin B_{12} levels seen over a 17-year period at two university hospitals showed that 39% of them had neurological disorders attributable to vitamin B_{12} deficiency [42]. Again and unfortunately, how many of them experienced hallucinations was not specified.

Diagnosis

Vitamin B_{12} levels are usually assessed through a serum vitamin B_{12} immunoassay (for an overview of four tests, see [62]). As mentioned above, cut-off values are slightly different for different tests and laboratories. However, even if thresholds were cast in concrete, interpreting them remains a challenge. Since they are based on mean values in the general population, taking cut-off values as absolutes may lead to an underestimation of clinically significant deficiencies in people with different metabolic requirements [8]. Moreover, since tests vary in their capacity to distinguish between biologically active and inactive cobalamin, screening for deficiencies may lead to false-negative findings to varying degrees across tests. Another point to be taken into consideration is that serum cobalamin levels are not equal to tissue levels. As a consequence, especially levels in the lower range of normal should not be taken at face value but instead be construed as "possibly deficient." Given these challenges, it has been proposed to replace serum cobalamin tests in routine clinical practice by holotranscobalamin and total homocysteine tests [63]. Nonetheless, serum cobalamin tests have remained the test of choice for most laboratories.

Another diagnostic pitfall is the assumption that testing for serum vitamin B_{12} might not be necessary once pernicious anaemia has been ruled out. As Pickett already remarked 120 years ago on the basis of 7 cases of pernicious anaemia, "when the spinal cord bears the brunt of the disease process in paresis, a simple anaemia with leucocytosis is found; when mental symptoms alone appear, the blood state is not characteristic" [64]. This early finding was tentatively confirmed by Ssonko et al. [65] who tested 280 psychiatric inpatients and found reduced levels of vitamin B_{12} in 29% of them with only a minority showing haematological abnormalities. In an older study, Hector and Burton cited 12 papers published between 1903 and 1924 – together reflecting on 111 patients with pernicious anaemia and psychiatric symptoms – which they labelled as "probable cases" of vitamin B_{12} deficiency [66]. Among

these 111 patients, only 11 (10%) had been described as suffering from hallucinations and/or delusions. Likewise, studying 20 patients with pernicious anaemia and psychiatric symptoms, Eilenberg found evidence of a direct relationship between the two conditions in only four people (20%) [67]. Together, these studies suggest that vitamin B_{12} deficiency can apparently target haematological and perceptual systems via different or at least diverging metabolic pathways. The nature of these pathways is in need of further study, but in clinical practice, these findings may serve as an extra incentive to test serum cobalamin levels even when haematological findings are normal. In addition, when a vitamin B_{12} deficiency seems likely, a further diagnostic workup may be necessary to identify underlying causes.

Treatment

From the 50 cases here reviewed, it can be inferred that the treatment of vitamin B_{12}-related hallucinations primarily involves the administration of cobalamin. Hallucinations have long been described as preceding other neuropsychiatric sequelae of vitamin B_{12} deficiency. Equally, they also tend to disappear first with cobalamin treatment [68, 69]. Some authors have a preference for a certain type of cobalamin (e.g., hydroxocobalamin, mecobalamin, cyanocobalamin), but empirical support for this is lacking. In most cases, cobalamin treatment is commenced intravenously or intramuscularly, but especially in the absence of malabsorption, this can be replaced by oral supplementation after several days [70]. Depending on the clinical context, adjuvant treatment may be indicated. Apart from pharmacotherapy (e.g., antipsychotic or antidepressant treatment), in designated cases also physiotherapy, psychotherapy, and/or psychoeducation may be needed. If the rare cases I reviewed are anything to go by, the success rate of cobalamin monotherapy tends to be substantial. Still, its efficacy is in need of further assessment through clinical and preferably double-blind and placebo-controlled trials.

Recommendations for Clinical Practice and Research

In most health services, the routine clinical workup of hallucinatory disorders and syndromes does not include the testing of vitamin B_{12}. This review indicates that it might be worthwhile to do so since the consequences for treatment may be considerable. Moreover, in the scheme of things, testing for vitamin B_{12} is hardly burdening and fast as well as inexpensive. Regarding treatment, even though cobalamin supplementation is not an evidence-based method, it may be taken into consideration under the following circumstances:

- Hallucinations associated with vitamin B_{12} deficiency
- Hallucinations in the presence of vitamin B_{12} serum levels in the lower normal range
- Hallucinations in the presence of normal vitamin B_{12} serum levels *and* elevated folate levels
- Hallucinations in the presence of normal vitamin B_{12} serum levels *and* a history of gastric or intestinal surgery
- Hallucinations of unknown origin
- Therapy-resistant hallucinations

Since the effects of cobalamin intoxication are minimal [71], the efficacy of such a regimen should be easily testable in a double-blind, placebo-controlled study. Preferably, such studies should also attempt to chart the order in which individual symptoms appear and disappear, so as to throw light on the brain areas that respond to cobalamin treatment, which may in turn be a stepping stone to unravelling underlying mechanisms.

Limitations

A major limitation of the present review is the small number of original reports that were available and suitable for inclusion. This is especially problematic in the face of the relatively high lifetime prevalence of vitamin B_{12} deficiency in the general population. Moreover, since reports on successful treatments tend to be published more readily than those describing unsuccessful treatments, the findings presented here might well reflect publication bias. Another limitation is that we currently have only partial insight into the metabolism of vitamin B_{12} and even less into the relationship between vitamin B_{12} deficiencies and hallucinations. This is at least partly due to a lack of systematic, and larger-scale, studies but also to the scope of most studies that did reach publication. After all, many of the case descriptions I reviewed lacked a systematic approach to hallucinations and other misperceptions. Only 40% contained phenomenological descriptions and none covered the full range of sensory modalities that might have been involved. Instead, most original reports focused on auditory and visual hallucinations (plus paraesthesia). Therefore, from the cases reviewed, it is hard to gain a reliable impression of the prevalence and full range of these hallucinations or to make inferences about the perceptual networks involved.

Conclusion

Having reviewed 50 case descriptions on hallucinations associated with vitamin B_{12} deficiency, I found that these phenomena tend to be well amenable to cobalamin treatment (either as adjuvant treatment or as

monotherapy). The hallucinations described are predominantly visual and/or auditory in nature, with 20% being specified as complex, compound, or panoramic. Considering the wider context of the neuropsychiatric sequelae of vitamin B_{12} deficiency, they tend to appear first and also tend to be the first to disappear with cobalamin treatment. Full amelioration of hallucinations was thus obtained in 75% of the cases reviewed and partial amelioration in the remaining 25%, all within an average time span of 2 months. Of note, a quarter of the cases involved therapy-resistant hallucinations that fully resolved under cobalamin monotherapy. Other neuropsychiatric manifestations of vitamin B_{12} deficiency tended to fully disappear in 60% of the cases. Comorbid pernicious anaemia was found in less than a third of the cases, suggesting the existence of two separate or partly overlapping pathways for perceptual and haematological symptoms of vitamin B_{12} deficiency, the nature of which is in need of further study. In the light of the high prevalence rate of vitamin B_{12} deficiency in the general population, the findings here presented should be interpreted with great caution. Nonetheless, they offer possibilities for further research and – in designated cases – application in clinical practice. This may be especially important given the recent increase in the popularity of vegetarianism and the recreational use of nitrous oxide.

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Statement of Ethics

An ethics statement is not applicable because this study is based exclusively on the published literature.

Conflict of Interest Statement

The author received publishing royalties for *A Dictionary of Hallucinations* (Springer Nature, 2010/2023), *Alice in Wonderland Syndrome* (Springer Nature 2020), *Katatonie en Dissociatie* (AccreDidact/Prelum, 2014), *Visuele Hallucinaties en Andere Positieve Visuele Waarnemingsstoornissen* (AccreDidact/Prelum, 2013), and *Hallucinations: Research and Practice* (Springer, 2012).

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Author Contributions

J.D.B. conceptualized and designed the study, collected data, interpreted the findings, and wrote the manuscript.

Data Availability Statement

All data generated or analysed during this study are included in this article and its supplementary material files. Further enquiries can be directed to the corresponding author.

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