Chapter 16

Medical Diseases and Others

CQ 16-1

What are the features of cognitive impairment due to vitamin deficiency?

Answer

Vitamin B_1 deficiency leads to the development of Wernicke encephalopathy, an acute metabolic encephalopathy with main symptoms of impaired consciousness, eye movement disorder, and motor ataxia. If not responding to treatment, Wernicke encephalopathy may convert irreversibly to Korsakoff syndrome and manifests symptoms such as disorientation, amnesia, confabulation (storytelling), and lack of disease awareness.

Vitamin B_{12} deficiency causes memory impairment and psychiatric symptoms, and folate deficiency has been reported to cause cognitive impairment similar to that of vitamin B_{12}. In recent years, vitamin D deficiency has also been suggested to cause cognitive impairment.

Comments and evidence

Vitamin B_1 deficiency is often caused by alcoholism or an unbalanced diet. As the condition progresses, patients develop Wernicke encephalopathy with the triad of impaired consciousness, eye movement disorders, and ataxic gait [1]. However, only few cases satisfy all the three main features. Other symptoms such as delirium, weakness, apathy, impaired recognition of the surrounding situation, and impaired concentration may also be observed; and may even lead to coma and death [2, 3]. It has been reported that Wernicke encephalopathy converts to Korsakoff syndrome in 85% of the cases. In these cases, memory impairment more severe than recent memory, anterograde amnesia, and confabulation are observed, but procedural memory is often preserved [3].

Vitamin B_6 deficiency can also cause pellagra-like symptoms (see below).

In vitamin B_{12} deficiency and folic acid deficiency, cognitive impairment may be caused by hyperhomocysteinemia.

In vitamin B_{12} deficiency, even in the absence of anemia and macrocytosis, cognitive impairments such as slowed thinking, memory impairment, and attention deficit; psychiatric symptoms such as depressive symptoms, delusions, hallucinations, and delirium; and neurological symptoms such as motor, sensational and autonomic symptoms are observed [4].

Although the neuropsychiatric symptoms in folate deficiency are the same as those in vitamin B_{12} deficiency, it has been reported that decrease in blood folate level is associated with cognitive impairment [5], but no consensus has been reached.

Niacin (nicotinic acid, nicotinamide) deficiency has been known as pellagra from the past (four "Ds": dermatitis, diarrhea, dementia, death) [6].

In recent years, vitamin D deficiency has been found to be quite common in older people. Although a meta-analysis has reported a relationship between low vitamin D and memory disorder and executive dysfunction [7], there is no consistent opinion.

References

1) Koyama K. Symptoms of Wernicke's encephalopathy. Vitamin. 2012; 86(11): 620-624. (In Japanese)
2) Sechi G, Serra A. Wernicke's encephalopathy: new clinical settings and recent advances in diagnosis and management. Lancet Neurol. 2007; 6(5): 442-455.
3) Kopelman MD, Thomson AD, Guerrini I, et al. The Korsakoff syndrome: clinical aspects, psychology and treatment. Alcohol. 2009; 44(2): 148-154.
4) Lachner C, Steinle NI, Regenold WT. The neuropsychiatry of vitamin B12 deficiency in elderly patients. J Neuropsychiatry Clin Neurosci. 2012; 24(1): 5-15.
5) Michelakos T, Kousoulis AA, Katsiardanis K, et al. Serum folate and B12 levels in association with cognitive impairment among seniors: results from the VELESTINO study in Greece and meta-analysis. J Aging Health. 2013; 25(4): 589-616.
6) Niwa A. Chapter 3 Diagnosis of dementia, 4 Examinations. Nakajima K (ed.) Dementia Handbook. Tokyo: Igaku Shoin; 2013: 131. (In Japanese)
7) Annweiler C, Montero-Odasso M, Llewellyn DJ, et al. Meta-analysis of memory and executive dysfunctions in relation to vitamin D. J Alzheimers Dis. 2013; 37(1): 147-171.

Search formula

PubMed search: June 27, 2015 (Saturday), July 21, 2015 (Tuesday)

#1 (("Dementia" [Mesh] OR dementia OR "Cognition Disorders" [Mesh] OR cognition disorder* OR "cognitive impairment") AND ("Avitaminosis" [Mesh] OR avitaminosis OR "vitamin deficiency")) OR (((("Thiamine" [Mesh] OR "Vitamin B 1" [TI] OR "Vitamin B1" [TI]) AND ("Korsakoff Syndrome" [Mesh] OR Wernicke Korsakoff Syndrome* [TI] OR Korsakoff Psychosis* [TI])) OR "Vitamin B 6" [Mesh] OR "Vitamin B 6" [TI] OR "Vitamin B6" [TI] OR "Vitamin B 6 Deficiency" [Mesh] OR "Vitamin B 12" [Mesh] OR "Vitamin B 12" [TI] OR "Vitamin B12" [TI] OR "Vitamin B 12 Deficiency" [Mesh] "Vitamin D" [Mesh] OR "Vitamin D" [TI] OR "Vitamin D Deficiency" [Mesh] OR "Folic Acid" [Mesh] OR "folic acid" [TI] OR folate [TI]) AND ("Executive Function" [Mesh] OR cognitive function* [TI]) OR (("Avitaminosis" [Mesh] OR avitaminosis [TI]) AND ("Hyperhomocysteinemia" [Mesh] OR hyperhomocysteinemia* [TI]) AND ("Cognition Disorders" [Mesh] OR "cognition disorder*" [TI] OR "cognitive impairment" [TI] OR "cognition disorder*" OR cognitive impairment" OR "cognitive decline" [TI]))

Ichushi search: June 27, 2015 (Saturday), July 21, 2015 (Tuesday)

#1 ((Dementia/TH OR Dementia/TI OR Cognitive impairment/TH OR Cognitive impairment/TI OR Cognitive decline/TI) AND (Vitamin deficiency/TH OR Vitamin deficiency/TI)) OR ((Cognitive impairment/TH OR Cognitive impairment/TI OR Cognitive decline/TI) AND (((Thiamine/TH OR Thiamine/TI OR Thiamin/TI OR Vitamin B1/TI OR "Vitamin B1"/TI OR "Vitamin B 1"/TI) AND (Korsakoff syndrome/TH OR Korsakoff syndrome/TI OR Korsakoff syndrome/TI OR Korsakoff psychosis/TI)) OR "Vitamin B6"/TH OR "Vitamin B6"/TI OR Vitamin B6/TI OR Vitamin B6 deficiency/TH OR "Vitamin B12"/TH OR "Vitamin B12"/TI OR Vitamin B12/TI OR Vitamin B12 deficiency/TH OR "Vitamin D"/TH OR "Vitamin D"/TI OR Vitamin D/TI OR Vitamin D deficiency/TH OR "Folic Acid"/TH OR "Folic Acid"/TI OR Folic acid/TI OR Folic acid deficiency/TH OR ((Vitamin deficiency/TH OR Vitamin deficiency/TI) AND (Hyperhomocysteinemia/TH OR Hyperhomocysteinemia/TI))))

CQ 16-2

What are the features of cognitive impairment due to hypothyroidism?

Answer

Overt hypothyroidism causes cognitive impairment and depressive symptoms. Many reports have shown no clear effect of subclinical hypothyroidism on cognitive function, but opinion is divided. In Hashimoto's encephalopathy, acute psychiatric symptoms such as impaired consciousness, delirium, and hallucination; cognitive impairment; and chronic symptoms such as depression and anxiety are observed. C

Comments and evidence

In overt hypothyroidism, a wide range of cognitive functions are impaired, and impairments of general intelligence, attention and concentration, memory, perceptual function, language, and executive function are observed. Especially, memory impairment and verbal memory are consistently reported [1-3]. Many studies have concluded that there is an association between overt hypothyroidism and depressive symptoms.

Subclinical hypothyroidism generally does not cause depressive symptoms, anxiety, or widespread or severe cognitive impairment, but no consensus has been established [2].

Hashimoto's disease (chronic thyroiditis) is the most common cause of hypothyroidism. In Hashimoto's encephalopathy, cognitive impairment, word-finding difficulty, epileptic seizures, behavioral disorders, myoclonus, gait ataxia, aphasia, tremor, hyperreflexia, motor deficit, psychotic symptoms, depressive symptoms, confusion, and sleep disorder have been reported [4]. In particular, patients who are positive for anti-N-terminal of α-enolase (NAE) antibody often presents with an acute encephalopathy type, with high frequencies of consciousness disturbance and various psychiatric symptoms and cognitive impairment. In contrast, patients with a chronic course often have depressive symptoms, anxiety, and cerebellar ataxia.

■ References

1) Japan Thyroid Association. Guidelines for the Diagnosis of Thyroid Diseases 2013. http://www.japanthyroid.jp/en/guidelines.html
2) Samuels MH. Psychiatric and cognitive manifestations of hypothyroidism. Curr Opin Endocrinol Diabetes Obes. 2014; 21(5): 377-383.
3) Dugbartey AT. Neurocognitive aspects of hypothyroidism. Arch Intern Med. 1998; 158(13): 1413-1418.
4) de Holanda NC, de Lima DD, Cavalcanti TB, et al. Hashimoto's encephalopathy: systematic review of the literature and an additional case. J Neuropsychiatry Clin Neurosci. 2011; 23(4): 384-390.
5) Yoneda M. Hashimoto's encephalopathy. Japanese Journal of Molecular Psychiatry (Bunshi Seishinigaku) 2013; 13(3): 178-184. (In Japanese)

■ Search formula

PubMed search: June 27, 2015 (Saturday), July 7, 2015 (Tuesday), September 12, 2015 (Saturday)

#1 (("Dementia" [Mesh] OR dementia OR "Cognition Disorders" [Mesh] OR "cognition disorder*" OR "cognitive impairment") AND ("Hypothyroidism" [Mesh] OR hypothyroid* OR "Hashimoto's disease" OR "Hashimoto disease")) OR (("Executive Function" [Mesh] OR "Cognition" [Mesh] OR cognitive function* OR "Cognition Disorders" [Mesh] OR cognition disorder* OR cognitive disorder* OR cognitive impairment*) AND ("Hypothyroidism" [Mesh] OR hypothyroid* OR "Hashimoto Disease" [Mesh] OR "hashimoto encephalopathy" OR "hashimoto's encephalopathy" OR Hashimoto's disease* OR Hashimoto disease*)) OR ("Thyroid Diseases/diagnosis" [Majr] AND manifestation [TI])

Ichushi search: June 27, 2015 (Saturday)

#1 (Dementia/TH OR Dementia/TI OR Cognitive impairment/TH OR Cognitive impairment/TI OR Cognitive decline/TI) AND (Hypothyroidism/TH OR Hypothyroidism/TI OR Hashimoto disease/TI)

CQ 16-3

What are the features of cognitive decline due to neurosyphilis?

Answer

Neurosyphilis is a neurological infection caused by *Treponema pallidum*, which infiltrates the nervous system after the initial infection. In late syphilis, which develops more than 15 to 20 years after the initial infection, long-term chronic meningovasculitis as well as the spread of infiltration and inflammation to the brain parenchyma, cause progressive paralysis manifesting with dementia, and tabes dorsalis due to damage of the dorsal funiculus and/or dorsal nerve roots. Dementia symptoms include disorientation, memory disturbance and judgment disability, as well as hallucination, delusion, irritability, and convulsion.

Comments and evidence

After infection occurs *via* sexual contact or blood transfusion, syphilis can infiltrate the central nervous system and cause progressive paralysis, mainly manifesting dementia 15-20 years after the initial infection. As a result of long-term chronic meningovasculitis, bacterial infiltration and/or inflammatory spread to the central nervous system, dementia symptoms in progressive paralysis are observed as disorientation, memory disturbance, and decline in judgment and calculation capacity, followed by manifestations of anti-social speech and behaviors and abnormal behaviors. Furthermore, patients show psychiatric symptoms such as hallucination, delusion, and depression. Symptoms are diverse, and it is difficult to distinguish neurosyphilis from other dementias. Clinical diagnosis is made by serum non-treponema tests such as VDRL and RPR, syphilis-specific antigen test (TPHA), and cerebrospinal fluid examination (TPHA and FTA-Abs in cerebrospinal fluid) [1, 2].

Treatment includes penicillin G (18-24 million units/day) administered by continuous intravenous infusion or intravenous infusion every 4 hours for 10-14 days. However, some patients show minor improvement with sequelae.

For details, refer to the "Guideline for Diagnosis and Treatment of Sexually Transmitted Diseases" (http://jssti.umin.jp/pdf/guideline-2011.pdf).

References

1) Clement ME, Okeke NL, Hicks CB. Treatment of syphilis: a systematic review. JAMA. 2014; 312(18): 1905-1917.
2) Ghanem KG. REVIEW: Neurosyphilis: a historical perspective and review. CNS Neurosci Ther. 2010; 16: e157-e168.

Search formula

PubMed search: June 30, 2015 (Tuesday)

#1 ("Neurosyphilis" [Mesh] OR neurosyphilis OR "general paresis" OR "progressive paralysis") AND ("Dementia" [Mesh] OR dementia[TI] OR "Cognition Disorders" [Mesh] OR "cognition disorder*" OR "cognitive dysfunction")

Ichushi search: June 30, 2015 (Tuesday)

#1 (Syphilis-nerve/TH OR Neurosyphilis/TI)AND(Dementia/TH OR Dementia/TI OR Cognitive impairment/TH OR Cognitive impairment/TI OR Cognitive function impairment/TI OR Cognitive decline/TI)

CQ 16-4

What are the features of cognitive impairment caused by hepatic encephalopathy (HE)?

Answer

In hepatic encephalopathy (HE), attention, information processing ability, and visuomotor coordination are impaired from an early stage. Occasionally these symptoms are accompanied by focal neurological signs such as parkinsonism and/or choreic movement.

Comments and evidence

HE is characterized as a group of neuropsychiatric symptoms caused by acute or chronic liver dysfunctions. HE occurs when the portal venous shunt produces toxic substances such as ammonia produced by hepatocellular injury, and the toxins enter the systemic circulation without detoxication in the liver [1, 2].

The current trend is to interpret the disease as a continuum and use the following clinical rating: (1) lack of cognitive impairment (UNIMPAIRED); (2) acute confusional syndrome (unstable); and (3) persistent chronic cognitive impairment (stable). In the continuous approach, patients may move from one situation to another interchangeably [3]. Severity is evaluated categorically and graded based on the state of consciousness, intellectual function, behavior, and neuromuscular signs into 5 stages (stage 0 to 4) [4].

Acute episodic HE is an acute confusional syndrome that can progress to coma in severe cases. Bilateral symmetrical hyperintensities in the globus pallidus and ventral midbrain are observed on T1-weighted MRI. In cases of acute exacerbation of chronic hepatitis, bilateral symmetrical hyperintensities have been observed in the thalamus, posterior limb of internal capsule, and white matter around the lateral ventricle on diffusion-weighted and fluid-attenuated inversion recovery (FLAIR) MRI.

Minimal HE is present in approximately 55% of cirrhosis patients. They show abnormalities on comprehensive neuropsychological test but not on neurological examination. It is associated with impaired driving skills and a significantly higher risk of motor vehicle crashes, due to attention and visuomotor coordination deficits.

Even in patients with prolonged chronic cognitive impairment, motor symptoms such as parkinsonism, choreic movements, and myelopathy are observed in the late stages.

■ References

1) Taniguchi E, Kawaguchi T, Sakata M, et al. Lipid prole is associated with the incidence of cognitive dysfunction in viral cirrhotic patients: a data-mining analysis. Hepatol Res. 2013; 43(4): 418-424.
2) Seyan AS, Hughes RD, Shawcross DL. Changing face of hepatic encephalopathy: role of inflammation and oxidative stress. World J Gastroenterol. 2010; 16(27): 3347-3357.
3) Cordoba J. New assessment of hepatic encephalopathy. J Hepatol. 2011; 54(5): 1030-1040.
4) Bajaj JS. Review article: the modern management of hepatic encephalopathy. Aliment Pharmacol Ther. 2010; 31(5): 537-547.

■ Search formula

PubMed search: June 30, 2015 (Tuesday)

#1 ("Hepatic Encephalopathy" [Mesh] OR "Liver Diseases/complications" [Mesh] OR "Liver Diseases" [Majr]) OR "hepatic encephalopathy" OR "liver dysfunction" [TI] OR liver disease* [TI]) AND ("Dementia" [Mesh] OR dementia [TI] OR "Cognition Disorders" [Mesh] OR "cognition disorder*" OR "cognitive dysfunction")

Ichushi search: June 30, 2015 (Tuesday)

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CQ 16-5

What are the features, diagnosis, and treatment strategies for dementia symptoms of idiopathic normal pressure hydrocephalus (iNPH)?

Answer

Psychomotor speed, attention, working memory, and memory function are the cognitive functions that tend to be impaired in iNPH and which can be improved by removing cerebrospinal fluid. For diagnosis and treatment strategy, refer to "Clinical Practice Guideline for Idiopathic Normal Pressure Hydrocephalus, 2nd Edition" (2011). B

Comments and evidence

In patients with iNPH, psychomotor speed decreases, and attention and working memory are impaired even in mild cases. For diagnosis and treatment policy, refer to the "Clinical Practice Guideline for Idiopathic Normal Pressure Hydrocephalus, 2nd Edition" (2011) [1].

■ References

1) Japanese Society of Normal Pressure Hydrocephalus, Clinical Practice Guideline for Idiopathic Normal Pressure Hydrocephalus Development Committee (Ed.) Clinical Practice Guideline for Idiopathic Normal Pressure Hydrocephalus, 2nd edition. Tokyo: Medical Review Co. Ltd.: 2011. http://minds.jcqhc.or.jp/n/med/4/med0038/G0000352/0001 (In Japanese)

■ Search formula

PubMed search: May 28, 2015 (Thursday)
#1 "Hydrocephalus, Normal Pressure" [Mesh] AND ("idiopathic normal pressure hydrocephalus" OR iNPH)

Ichushi search: May 28, 2015 (Thursday)
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