Subacute sclerosing panencephalitis in a child with celiac disease – A rare association

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ABSTRACT

Celiac disease (CD) is an immune-mediated disease with varied intestinal and extraintestinal manifestations. Among extraintestinal manifestations, neurological conditions are being reported with increased frequency nowadays. We report a child of CD with progressively increasing dementia, poor scholastic performance, and myoclonic epilepsy. On further investigation, the cause of neurological manifestations was diagnosed as subacute sclerosing panencephalitis (SSPE). It is a slowly progressive neurodegenerative disorder caused by defective measles virus which is eventually fatal. The coexistence of CD and SSPE could not be found in literature.

Key words: *Celiac disease, Subacute sclerosing panencephalitis, Neurodegenerative disorder*

Celiac disease (CD) is an immune-mediated disease occurring in genetically susceptible individuals following exposure to gluten found in wheat, rye, and barley. It is reported to have neurological manifestations. Some common manifestations are epilepsy, peripheral neuropathy, cerebellar ataxia, progressive leukoencephalopathy, cerebral vasculitis, dementia, chorea, brain stem dysfunction, myelopathy, mononeuritis multiplex, and Guillain–Barre-like syndrome [1].

We describe a case of CD who developed neuroregression with myoclonic seizures which were later diagnosed as subacute sclerosing panencephalitis (SSPE). It is a neurodegenerative disorder caused by defective measles virus. A case has been reported where CD and SSPE coexisted and there may be an impact of CD on the clinical course of SSPE. Furthermore, by this case report, we describe the possible neurological manifestations in a CD patient.

CASE REPORT

An 8-year-old female child presented to the department of pediatrics of a tertiary hospital of North India with 9 months history of progressively increasing dementia, poor scholastic performance, and myoclonic epilepsy. Dementia was initially in the mild form depicted by forgetting small things such as her way to home/school/playground and forgetting tables. However, gradually, it progressed further so that the patient was not even able to recognize the family members. Seizure frequency increased from 1–2 episodes per week to 8–10 episodes per day. The child had emotional instability in the form of excessive, inappropriate laughing along with the repetition of action and words, and irrelevant talking. She also developed bowel and bladder incontinence.

She had recurrent episodes of diarrhea since she was 7 months old. She was diagnosed as a case of CD 8 months back with elevated immunoglobulin A anti-tissue transglutaminase (tTG) antibody level (204.8 U/mL) in serum and duodenal biopsy showing severe villous blunting with a significant increase in intraepithelial lymphocytes (Marsh score 3c). Although advised, the child did not follow a gluten-free diet. She was unimmunized and there was a history of measles at 5 years of age.

On examination, the child had stable vitals, unremarkable general physical examination, normal facies, and absence of neurocutaneous markers. Her weight was 16 kg against expected of 24 kg (<3rd centile, underweight) and height was 110 cm against expected of 125 cm (<3rd centile, stunted). The child was hyperactive and unable to follow simple commands. Other neurological and systemic examination findings were normal.

A provisional diagnosis of CD with the neurodegenerative disorder was made. Neurological manifestations could be due to CD itself or other causes such as SSPE, neuronal ceroid lipofuscinoses, or Wilson's disease. Fundus examination was normal. There were no abnormal findings on magnetic resonance imaging brain. Electroencephalogram (EEG) revealed generalized spike and wave epileptiform discharges. Urinary copper excretion at 24 h was normal and no Kayser–Fleischer ring was seen on slit-lamp examination. Serum Vitamin B12 and folate levels were 634 pg/mL and 13.6 ng/mL, respectively, which were within normal limits.

Human immunodeficiency virus (HIV) serology was non-reactive. Serum and cerebrospinal fluid (CSF) anti-measles antibody titers were ≥1:512 and 1:16, respectively, suggestive of SSPE (raised anti-measles antibody titers of 1:256 or greater in serum and 1:4 or greater in CSF is diagnostic of SSPE). The ratio of CSF anti-measles antibody titer to serum titer in the patient was 1:32 which was raised (ratio of CSF titer to serum titer in SSPE ranges from 1:4 to 1:128).

The child was kept on strict gluten-free diet and sodium valproate was given to control seizures following which there was improvement within 2 weeks. There was an improvement in behavior, a decrease in seizures and bladder and bowel control was restored. However, this improvement could be sustained for only 1 month. Despite good compliance to antiepileptic therapy and strict gluten-free diet, patient's neurological status deteriorated. Isoprinosine was started and antiepileptic drug dose was also increased, but there was no improvement. The patient was eventually lost to follow-up after 6 months.

DISCUSSION

CD is a chronic, multifactorial, and autoimmune disease with a strong human leukocyte antigen association that occurs in 1% of the population. It occurs following exposure to the glutens and has both intestinal and extraintestinal manifestations. One of the most important extraintestinal manifestations is the neurological symptom such as epilepsy, cerebellar and myoclonic ataxia, peripheral neuropathy, cerebral vasculitis, dementia, chorea, brain stem dysfunction, myelopathy, and Guillain–Barre-like syndrome [1]. CD may also cause chronic headaches, learning disorders, and attention-deficit/hyperactivity disorder [2].

A number of hypotheses have been proposed for the pathogenesis of neurological manifestations in CD, namely, antibodies against gliadin, ganglioside, tTG, and vitamin deficiencies due to malabsorption, and direct neurotoxic effect of gluten [3-5]. The most recent hypothesis suggests that different manifestations of gluten sensitivity depend on the role of TG antibodies in the humoral immune response. Different TG may lead to lesions in different body sites [5]. TG 2 is considered the autoantigen in classic intestinal CD, whereas TG3 has a role as the autoantigen in dermatitis herpetiformis and TG 6 is important in brain damage. Most of the cases have not shown improvement in neurological signs and symptoms to gluten-free diet as reported by many authors [6-10]. Literature search did not reveal any case report of neuroregression in CD.

SSPE is a progressive, long-term fatal complication of measles virus infection manifesting as changes in personality and behavior, seizures, dementia, extrapyramidal symptoms, and progressive unresponsiveness. Its pathogenesis remains unclear although it has been attributed to defective measles virus, immature immunity, and autoimmunity [11,12]. Diagnosis is made by its characteristic clinical presentation, periodic EEG complexes, and elevated measles antibody titers in serum and CSF, as shown in this case. The survival period following the onset of symptoms is few years.

Our patient was a case of CD diagnosed on the basis of typical gastrointestinal symptoms, raised antibody titer and typical small intestinal biopsy findings who presented with neuroregression and epilepsy. CD itself was kept as the first possible cause of neuroregression but due to a positive history of measles in the patient and non-availability of supporting data, the patient was further evaluated for SSPE and other possible causes of neuroregression too. SSPE was diagnosed on the basis of raised anti-measles antibody titers in blood and CSF.

On starting a gluten-free diet and antiepileptic drug, the patient showed transient improvement, thus pointing toward the possible contribution of the CD itself to neurological manifestations. However, the patient started deteriorating again on further follow-up suggesting the typical slowly progressive course in SSPE. Muthusamy *et al*. reported a case of SSPE in HIV patients [13]. Baldolli *et al.* and Hughes *et al.* reported cases of SSPE in immunosuppressed patients [14,15]. Association of CD and SSPE could not be found in literature. Hence, the interaction of the two pathophysiologically different disease entities is not known.

CONCLUSION

Although there are various recommendations on screening of children with neurological manifestations for CD as well as screening of neurological manifestations in CD patients, no consensus has been made until now. With an increasing number of CD cases being diagnosed nowadays, such consensus is needed.

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