Transverse Myelitis as Manifestation of Celiac Disease in a Toddler

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We present a 17-month-old girl with rapidly progressive unwillingness to sit, stand, play, and walk. Furthermore, she lacked appetite, vomited, lost weight, and had an iron deficiency. Physical examination revealed a cachectic, irritable girl with a distended abdomen, dystrophic legs with paraparesis, disturbed sensibility, and areflexia. An MRI scan revealed abnormal high signal intensity on T2-weighted images in the cord on the thoracic level, without cerebral abnormalities, indicating transverse myelitis (TM). Laboratory investigations revealed elevated immunoglobulin A antibodies against gliadin (1980.0 kU/L; normal, 0–10.1 kU/L) and tissue transglutaminase (110.0 kU/L; normal, 0–10.1 kU/L). Gastroscopy revealed villous atrophy in the duodenal biopsies and lymphocytic gastritis according to Marsh IIIb, compatible with celiac disease (CD). After the start of a gluten free diet and methylprednisolone, she recovered completely. To our knowledge, this is the first pediatric case of TM as manifestation of CD. We suggest that all children with TM or other neurologic manifestations of unknown origin should be screened for CD.

Celiac disease (CD) is an inflammatory condition of the small intestine, triggered by the ingestion of gluten.[1] It is the most common genetically food-based intolerance,[2] and 1 of the most common chronic diseases in childhood[1] (0.4%–1.3%[3]). The typical presentation involves gastrointestinal symptoms such as abdominal pain, chronic and/or intermittent diarrhea, or constipation. However, atypical or extraintestinal manifestations, such as fatigue, iron deficiency anemia, dental enamel hypoplasia, low bone mineral density, isolated elevation of aminotransferase levels, and short stature, seem to become more common and are more prevalent when age increases in children.[2] Neurologic complications are reported in 8% to 26% of adults with CD.[3–5] In children with CD, the risk of developing neurologic complications is lower.[3] Neurologic complaints may even be the first manifestation of CD, also in the absence of intestinal pathology.[6]

CASE REPORT

A 17-month-old girl was admitted to our hospital because of unwillingness to sit, stand, play, and walk. These complaints started at the age of 15 months during a period of illness, but were now rapidly progressive. Before presentation, she was a healthy toddler, with a normal growth and development. Pregnancy and birth were uncomplicated (at term, weight 3500 g). She was vaccinated according to the National Dutch program and received her last vaccination at the age of 14 months. Gluten was introduced at the age of 7 months. Since the age of 15 months she lacked appetite, vomited frequently, and lost 1 kg of weight, which started after an upper airway tract infection accompanied

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Dr Krom drafted the initial manuscript; Dr Sprangers treated the patient and reviewed and revised the manuscript; Drs van den Berg and Benninga reviewed and revised the manuscript; Dr Kindermann treated the patient and followed her and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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by a gastroenteritis. There was no fever or abdominal pain. Defecation was variable in frequency (once in 5 days up to once a day), with a normal to hard consistency without blood in the stools. In addition to her complaints, an iron deficiency (iron 4.3 μmol/L) was diagnosed, for which iron supplementation was started. Family history revealed hay fever and rubber allergy in mother, and asthmatic disease in father.

At physical examination, a cachectic, irritable, crying girl was seen (height –1.9 SD; weight –3.0 SD; weight for height –2.1 SD). Her abdomen was distended with loose abdominal skin. Peristalsis was normal and no defense or hepatosplenomegaly was found. Legs and buttocks revealed muscle wasting. At neurologic examination, a paraparesis, disturbed sensibility, and areflexia of both legs were found, without Babinski sign. There was no paraparesis of the arms, with normal reflexes.

An MRI scan of cerebrum and spinal cord revealed abnormal high signal intensity at the thoracic level, most prominent on the axial T2-weighted images at Th9 (Fig 1). On the sagittal T2-weighted images, swelling of the lower spinal cord up to the conus level was noticed with increased signal intensity (Fig 2). Cerebral findings were normal.

The complaints of constipation and paraparesis with areflexia of the legs in combination with imaging findings were suspected for a low-grade process or a (post)infectious or inflammatory origin, such as transverse myelitis (TM). An acute disseminated encephalomyelitis was less probable because of normal cerebral imaging.

Chest radiograph and repeated ultrasounds revealed neither masses, paraaortal lymphadenopathy, nor metastases. The tumor marker β-human chorionic gonadotropin was absent. Catecholamines vanilglycolic acid and vanilacetic acid were normal, which excluded neuroblastoma. Immunoglobulin (Ig)A (1.63 g/L; normal 0.12–1.6 g/L) and IgM (1.0 g/L; normal 0.09–0.74 g/L) were elevated. Due to supplementation, the iron status was improved but still decreased. Levels of creatine kinase (416 U/L; normal, 0–250 U/L) and creatine kinase-MB (13.8 μg/L; normal 0–5.2 μg/L) were elevated. Albumin was below normal range (32 g/L; normal 37–55 g/L). Antinuclear antibodies and extractable nuclear antigens were not found.

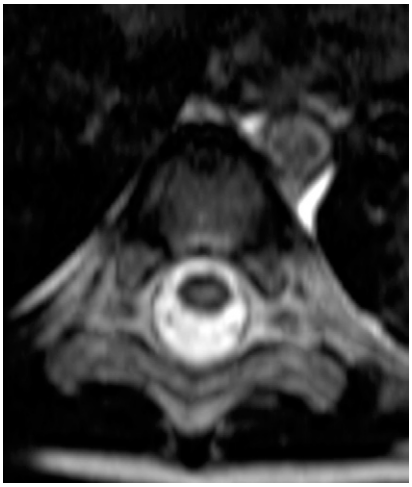

FIGURE 1
MRI spinal cord: axial T2-weighted image. T2-weighted axial image at the Th9 level reveals high signal intensity in the central part (white matter) of the spinal cord.

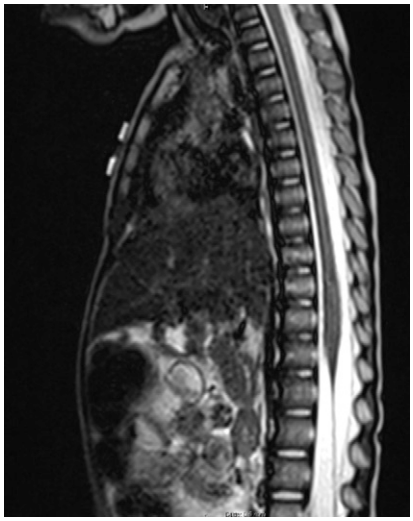

FIGURE 2
MRI spinal cord: sagittal T2-weighted image. On the sagittal T2-weighted images, swelling of the lower spinal cord up to the conus level was noticed with increased signal intensity.

Further studies (complete blood cell count, electrolytes, ureum, glucose, elastase, aspartate transaminase, alanine transaminase, alkaline phosphatase, amylase, lactate dehydrogenase, thiamine, free thyroxine, thyrotropin, thyroxine-binding globulin, reverse T3, IgG, cytomegalovirus-, Epstein-Barr virus-, and *Mycoplasma* serology and urine analysis) were normal.

Cerebrospinal fluid (CSF) was clear and had neither erythrocytes nor leukocytes, a normal level of protein and glucose, normal IgG and IgM indexes, and no oligoclonal bands. It was negative for Parecho-, Entero-, varicella zoster, herpes zoster, and adeno- and rotavirus, and in addition culture revealed no growth.

Although CSF was normal, due to the rapidly progressive neurologic symptoms in combination with the MRI findings, she was given a diagnosis of TM. Considering TM can be seen in the context of neuromyelitis optica, the ophthalmologist was consulted, but no signs of neuritis optica were found. Intravenous methylprednisolone therapy was started for TM with a high dose of 30 mg/kg for 3 days, followed by a 6-week reduction phase.

Further investigation revealed highly elevated IgA antibodies against tissue transglutaminase (1980.0 kU/L; normal 0–10.1 kU/L) and gliadin (110.0 kU/L; normal 0–10.1 kU/L). Additional gastroscopy revealed subtotal villous atrophy in the duodenal biopsies and lymphocytic gastritis according to Marsh IIIb.

The diagnosis of CD was made, and a gluten free diet (GFD) was started. Additional nocturnal tube feeding was started due to her failure to thrive and low oral intake.

After starting methylprednisolone treatment and GFD, her symptoms started to improve. She gained weight, was able to sit, became less irritable, and at the age of 17.5 months (2 weeks after admittance) she was discharged.

At the age of 18 months she was able to stand and walk, and neurologic examination was completely normal. A control MRI scan revealed normalization of earlier diagnosed spinal cord abnormalities. CSF again was normal.

To date our patient is 9 years old and is still on a GFD without symptoms of TM. When she eats gluten by accident, she immediately starts to vomit and gets diarrhea. Growth and psychosocial development are normal.

DISCUSSION

To our knowledge, this is the first pediatric case describing TM in the context of CD.

TM in children is a rare (0.4:1 000 000/year[7]) heterogeneous group of inflammatory disorders characterized by (sub)acute bilateral motor, sensory, and autonomic spinal cord dysfunction,[7] induced by an interruption of neuroanatomical pathways in the transverse plane of the spinal cord.[8] In children, there are 2 peaks of incidence, toddlers under the age of 3, and children between 5 and 17 years.[9]

In general, TM may be seen in relation to infection, vaccination, intoxication, autoimmune disease (eg, systemic lupus erythematosus, antiphospholipid syndrome, Sjögren syndrome, mixed connective tissue disease, and systemic sclerosis),[7] acquired demyelinating disease (eg, multiple sclerosis), the spectrum of disorders related to neuromyelitis optica, or may be categorized as idiopathic.[8] The prognosis depends on the cause of TM, and therefore is highly variable.[8] TM after infection or vaccination and idiopathic forms are usually monophasic, whereas TM in relation with multiple sclerosis and neuromyelitis optica are relapsing diseases associated with high risk of future attacks of TM and other neurologic events.[8]

TM as manifestation of CD has not been described earlier, and to date only 1 adult patient with CD has been reported to have TM.[10] Interestingly, both TM and CD are related with other autoimmune diseases,[2,7] and besides TM other neurologic complications and manifestations of CD have been described in children.[3–5,11–18] However, the pathogenesis of neurologic disturbances in patients with CD remains unknown,[4] but seems to be multifactorial.[3] Basically, nutritional, toxic, metabolic and immunologic factors, and direct harm by gluten were hypothesized to cause neurologic symptoms due to CD.[11]

Few data are available regarding neurologic conditions associated with CD in children.[4] A meta-analysis and systematic review by Lionetti et al[3] of 15 studies revealed an increased risk to develop neurologic complications, such as headache, peripheral neuropathy, and white matter disease in children with CD, but this risk was lower than in adults.

It has been hypothesized that white matter lesions are caused by ischemia due to vasculitis or as inflammatory demyelination due to an underlying autoimmune process.[5]

Neurologic symptoms as first manifestation of CD in children are even more unusual than complications.[11] Nevertheless, several pediatric cases of CD[11–18] (all confirmed with biopsy except for 1 patient due to young age[16]), with varying neurologic presentations have been described, such as headaches,[12] opsoclonus-myoclonus,[13] recurrent optic neuritis in the context of psoriasis and partial IgA and IgG3 deficiency,[14] recurrent acute encephalopathy,[11] status epilepticus/encephalopathy,[15] peripheral neuropathy,[17] recurrent transient hemiplegia with infarction of the brain,[18] and 2 children with cerebral venous sinus thrombosis.[16] A GFD alone[12,17] or combined with other treatments[11,13,15,16,18] led to improvement[13,18] or even complete resolution[11,12,15–17] of the various neurologic symptoms in these pediatric CD cases.

Although more cases of neurologic manifestations of CD with and without intestinal symptoms have been described in children,[11–18] the question whether these cases are caused by CD or are a rare coincidental cooccurrence, remains. A meta-analysis evaluated the association of CD and epilepsy and concluded that this association is probably a chance association.[3]

Despite extensive investigation for other causes, no other explanation than CD was found to cause TM in our patient. We hypothesize that TM in our patient was due to an autoimmune reaction caused by CD. In general, it has been hypothesized that an (auto-)immune phenomenon is causing the neurologic presentation of CD as well.[11–18] Both TM and CD are known to be seen in relation with other autoimmune diseases.[2,7] In children, 60% of TM cases occur due to an autoimmune phenomenon after infection or vaccination.[8]

CONCLUSIONS

We hypothesize that TM in our patient was due to an autoimmune reaction caused by CD, especially considering the clinical response on methylprednisolone and a GFD. In general, compliance to a strict GFD in patients with CD typically results in a complete return to health.[2] Although variable results of GFD have been shown in patients with CD with neurologic presentation, in several patients it has led to

regression or complete resolution of neurologic complaints. Therefore, we suggest that all children with TM, or other neurologic manifestations of unknown origin, should be screened for CD. More studies are needed to elucidate the exact pathogenesis and the effect of GFD in neurologic manifestations and complications of CD in children.

ABBREVIATIONS

CD: celiac disease
CSF: cerebrospinal fluid
GFD: gluten free diet
Ig: immunoglobulin
TM: transverse myelitis

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