Case Report

The Gut–brain Axis: A New Pathogenic View of Neurologic Symptoms – Description of a Pediatric Case

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Recent literature data have given emphasis to the relationship between gastrointestinal (GI) disorders and neurologic diseases, underlying a new pathogenic pathway: the so-called “gut–brain axis.” Herein, authors report a case of a 10-month-old male infant, admitted for drug-resistant epilepsy, associated with irritable behavior and GI discomfort, secondary to cow’s milk protein allergy. Seizures were described by parents as upward eye movements that were mostly deviated to the right and were associated with slight extension of his neck. They were infrequent at first, but had increased gradually during the course of 3 days (up to 15–20 times/day). No anticonvulsant therapy was effective. Only a cow’s milk protein-free diet, accidentally started during a gastroenteritis episode, was effective in stopping seizures. Our case underlines the peculiar vulnerability of the blood–brain barrier under 1 year of age, for which children of this age group experience neurologic manifestations during episodes of systemic inflammation.

Keywords: Food allergy, gastrointestinal inflammation, gut–brain axis, seizures

INTRODUCTION

Recent literature data have given emphasis to the relationship between gastrointestinal (GI) disorders, especially those with an immunologic pathogenesis and neurologic diseases, underlying a new pathogenic pathway: the so-called “gut–brain axis.” In regards, different hypotheses have been postulated, but the most debated is the one referred to the blood–brain barrier (BBB) disruption, both for genetic predisposition and secondary to peripheral inflammation.

Under a clinical point of view, there are some reports describing the central nervous system (CNS) involvement in patterns of peripheral systemic inflammation, such as atopy, including allergy to both inhalants and food, and bowel inflammatory diseases.

Herein, authors report a case of an 10-month-old male infant, admitted for drug-resistant epilepsy, associated with irritable behavior and GI discomfort, secondary to cow’s milk protein allergy.

Case Report

A 10-month-old male infant was admitted to the pediatric neurology practice at Maine Medical Center, Portland, Maine, United States, for experiencing very brief episodes of upward eye movements from 3 days before admission. Episodes were described by parents as upward eye movements that were mostly deviated to the right and were associated with slight extension of his neck. They were infrequent at first, but had increased gradually during the course of 3 days (up to 15–20 times/day). Occasionally, these episodes would have been accompanied with a slight imbalance. These episodes were accompanied by longer “absence” episodes of staring and unresponsiveness, which lasted about 2 min each and appeared during wakefulness.
Past history of the patient was unremarkable other than the fact that he was described as being colicky and underweight for his age, and he was being treated unsuccessfully with anti-reflux medication due to this reason. Other than that, he had normal developmental history. He had started walking prior to 10 months of age; he comprehended his mother’s words and was able to follow some simple commands. His allergy history was positive on amoxicillin (which had resulted in rash previously). Family history of epilepsy was negative.

At the time of admission, his physical examination suggested well-developed and well-nourished toddler. No head and neck abnormality was observed. Cardiovascular, pulmonary, abdominal, and musculoskeletal features were all at normal status.

Neurological examination revealed one brief episode of transient upward eye deviation noted with slight retropulsion. Cranial nerves were evaluated as normal. He had symmetrical 2+ deep tendon reflexes with flexor plantar responses. His gate and coordination were appropriate according to his age.

At the first admission, the patient underwent an electroencephalography (EEG) study during waking, which revealed frequent high-amplitude generalized epileptiform discharges, as well as intermittent right and left independent epileptiform discharges. The background EEG activity at time in between the epileptiform discharges appeared normal. During this study, at wakening, no seizures were visually recorded.

This EEG study was obtained with the 10–20 International system of electrode placement; 17 channels of continuous EEG were recorded digitally, with one channel of EKG. In the waking state, a normal posterior background rhythm was noted of high amplitude. The patient progressed from the waking to drowsy states and attained Stage II sleep, as evidenced by the presence of vertex sharp waves and sleep spindles. Throughout the sleeping recorded, high-amplitude generalized spike-waves discharges occurred singly. Independent right and left epileptiform discharges were also recorded. Sleep spindles and vertex sharp waves were not seen during the sleeping record. During waking, the record normalized significantly with a normal 4–5 cps background. Photic stimulation produced no activation of the recording. The neurophysiologist therefore concluded that the EEG was consistent with a generalized epilepsy, most probably of genetic and/or idiopathic origin.

According to the aforementioned proceedings, the infant was diagnosed with early-onset generalized epilepsy. He was started on levetiracetam 80 mg BD (oral), pyridoxine 50 mg daily, and diazepam 10 mg gel, 5 mg to be administered for seizures lasting more than 3 min.

At follow-up visits, brain magnetic resonance imaging (MRI) (without contrast) and genetic testing were ordered for further evaluation. Brain MRI showed normal brain structure. Genetic testing (STAT epilepsy panel, gene epilepsy testing including tests for the following genes: ALDH7A1, ARX, CDKL5, FOLR1, KCNQ2, KCNQ3, KCNT1, MECP2, MEF2C, PCDH19, PNPO, POLG, SCN1A, SCN1B, SCN2A, SCN8A, SLC2A1, SLC6A8, SPTAN1, STXBP1, TSC1, TSC2. These for inclusion and/or exclusion of the following genetic syndromes: Alpers syndrome, typical and atypical Rett syndrome, benign familial neonatal seizures, benign familial neonatal-infantile seizures, early-onset epileptic encephalopathy [infantile spasms], X-fragile syndrome, glucose transporter Type I deficiency syndrome, Ohtahara syndrome, progressive myoclonic epilepsy, pyridoxine-dependent seizures, and West syndrome) revealed that the infant was heterozygous for a single variant of uncertain significance in the POLG gene. No second pathogenic variant was identified by sequencing and deletion/duplication analysis of POLG.

Two months after starting the treatment, still there was no improvement in the child’s episodes, and during this time, he continued to have 15–30 seizures per day, which remained unresolved to increasing medication dose.

At this point, he developed a viral infection, which made him unable to eat any solid food or drink milk. His mother noticed that, although the child had consistent fever and was severely dehydrated for over a week, his seizures had stopped. She suspected a cow milk allergy, and subsequently eliminated all cow milk products from child’s and her own diet (because at this point, the child was still breastfed as well as consuming formula) after the child’s resolution from infection. Moreover, the child’s mother referred that seizures started after she was transitioning from breast milk feedings and supplementing his diet with milk-based formula. She described that, after several months of receiving milk products, the child presented irritable and distressed, for a lengthy period of time, with episodes of chronic diarrhea.

Interestingly, after a cow’s milk protein-free diet, the episodes did not occur any more. Afterward, the mother discontinued levetiracetam gradually. No seizures recurred ever since. A follow-up EEG, after cow’s milk protein-free diet, also proved as normal. Therefore, after approximately 2 months, the patient was diagnosed with drug-resistant seizures due to allergic reaction to milk protein, which only responded to milk-free diet.
Thereafter, the mother noticed a resolution of irritability, GI distress, and personality improvement in child as well as weight gaining. Therefore, the child is still continuing a cow’s milk protein-free diet, in view of future desensitizing therapy.

The child then underwent an allergic diagnostic workup, but one-hand skin-prick tests and radioallergosorbent test were negative.

**DISCUSSION**

Herein, the authors present a case of a 10-month-old male child with drug-resistant epilepsy, who underwent an important diagnostic workup before having a diagnosis of cow’s milk protein allergy. This case underlines two important topics: the first is the relationship between GI diseases and seizures, often discussed in literature as “gut–brain axis;” the second is the peculiar vulnerability of the BBB under 1 year of age, for which children of this age group experience neurologic manifestations during episodes of systemic inflammation.

In literature, other similar cases have been described, such as that one of Falsaperla et al., and Vitaliti et al.,[1] in which authors suggested that a peripheral inflammation of the GI tract can trigger the GI immune system, with an allergen-mediated activation of local antigen-presenting cells, consequent shift toward Type-II helper T-lymphocytes (Th2) and subsequent secretion of pro-inflammatory cytokines. These pro-inflammatory agents can diffuse in circulation, reaching the BBB and being responsible for its disruption, by mast cells’ activation and in loco induction of T-lymphocytes, with consequent CNS inflammation-triggering seizures.[1] Moreover, cow’s milk proteins can cause a GI inflammation responsible for the induction of T-lymphocytes specifically sensitized to these proteins, which migrate within the BBB in the context of the “homing” process.[9] Therefore, the absorption of cow’s milk proteins through an inflamed GI mucosa, with a consequent migration in the systemic circulation, may trigger those sensitized lymphocytes within the BBB (which had colonized it after a process of homing), with secondary induction of the inflammation cascade in the CNS.[1]

Literature data have been published on the role of pro-inflammatory cytokines in the “gut–brain axis.” In regards, tumor necrosis factor-alpha (TNF-alpha) was identified in a model of microglial-dependent, TNF-mediated increase of CNS excitability in mice, in which seizures were trigged by a 2,4,6-trinitrobenzene induced-colitis.[8] Other studies showed a pro-convulsing role for interleukin (IL-1b), with IL-1 receptor antagonist mainly playing an anticonvulsant action.[10-13] Taken together, all these data suggest that a peripheral inflammation involving the GI tract, such as that one described in food allergy and/or in inflammatory bowel diseases, can systemically widespread, involving other anatomic systems such as the nervous system.

In our case, the child presented with a positive neurologic clinical examination for focal myoclonic epilepsy, associated with paroxysmal events at EEG during critical events and during sleep, but not during physiological wakefulness. These events were related to cow’s milk protein consumption.

Another interesting topic is that seizures were the first clinical manifestation of cow’s milk allergy of both cases described by Falsaperla and Vitaliti and both children in those cases had the onset of their symptoms before 1 year of life. In regards, literature data have reported a peculiar frailty of the CNS to seize susceptibility, in children <12 months of age. The occurrence of simple febrile seizures in this age group has been associated with a statistically significant increase in the risk of subsequent epilepsy in some pediatric studies.[14-18] Moreover, the incidence of simple febrile seizures under the age of 12 months has been recognized as a risk factor for developing complex febrile seizures and/or epileptic syndromes in later years.[18] Therefore, the 1st year of life seems to be a critical period for the development of the CNS, and pathogennoxae-triggering inflammation may be responsible for any alteration in the development of the BBB. Nevertheless, further studies have to explain risk factors linked to the BBB vulnerability during early infancy.

Finally, it has to be mentioned that our patient underwent a complex diagnostic workup, with a final diagnosis accidentally given by an ex adiuvantibus therapy, and even when standard allergic tests were normal, highlighting a non-IgE-mediated food reaction. Therefore, first of all, this case suggests giving importance of familial and personal history to any allergic anamnesis and not to exclude any kind of sensitization only by standard tests, because even when negative, they cannot exclude non-IgE-mediated hypersensitivity reactions.

In fact, there are no available markers allowing a prompt diagnosis of these conditions. Some biological markers have recently been proposed, such as the dosage of the zonulin protein, a molecule that modulates the permeability of tight junctions between cells of the wall of the digestive tract and/or the cytokines’ pattern study. Nevertheless, these markers are not disease specific, and they can be altered in different inflammatory conditions.
Therefore, authors suggest that new research efforts should be addressed to the study of pathognomonic biological markers, specific for the diagnosis of seizures associated with systemic inflammation.

Conclusions

Similar cases have been described by our research group,[19,20] reinforcing the importance of the pathogenic pathway of the gut–brain axis. This pathway is the object of new research literature data and has to be explored further. Nevertheless, we think that GI diseases, as far as peripheral inflammation, have to be included in the diagnostic workup of those epileptic syndromes not responsive to conventional treatment. In regards, health-care assistants should also exclude an immune-mediated origin of neurologic symptoms.

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Conflicts of interest

There are no conflicts of interest.

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