Low Prevalence of Neurologic and Psychiatric Manifestations in Children with Gluten Sensitivity

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Objective To determine the frequency of neurologic manifestations in children with gluten sensitivity (GS) and the frequency of GS in children with neurologic disease.

Study design A total of 835 children with GS (based on positive titers for serum anti-gliadin antibody [AGA], anti-endomysial antibody [EMA], and anti-tissue transglutamine [tTG] antibody and a positive gut biopsy), representing the local childhood GS population in the town of Catania, Italy, were recruited, prospectively followed up, and screened for neurologic and psychiatric disturbances between 1991 and 2004. Serum AGA, EMA, and anti-tTG antibody titers were estimated in a prevalence sample of 630 consecutive children with neurologic disorders of unknown cause despite full investigation, 300 children with known neurologic syndromes, and 300 healthy children who served as controls. Statistical significance was assessed by the χ^2 test and Yates' χ^2 test.

Results Neurologic or psychiatric problems were noted in 15 of 835 children with GS (1.79%) with previously diagnosed GS enteropathy (GSE). In 7 of 630 children (1.1%) with a cryptogenic neurologic disorder, GS was identified based on GS autoantibody screening. These 22 children had febrile seizures, epilepsy, headache, mental retardation, neuropathy, and bipolar disorder; no children had ataxia or cerebellar disturbances. The HLAs were DQ2 (n = 16), DQ8 (n = 4), and DQ2/DQ8 (n = 2). Two of the 300 healthy controls (0.66%) had GS.

Conclusions Based on our findings, the prevalence of neurologic/psychiatric manifestations in this group of children with GS was low but slightly higher than that in the controls ($P = .041$). Children with known ($P = .772$) and cryptogenic ($P = 1.0$) neurologic disorders did not exhibit a higher prevalence of GS. *(J Pediatr 2008;152:244-9)*

Gluten sensitivity (GS) is an immune-mediated disorder triggered by the ingestion of gluten (a protein found in cereals, such as wheat, rye, and barley) in genetically susceptible individuals expressing the HLA class II molecules DQ2 or DQ8.[1-3] In its classic-onset form (starting at age 6 to 24 months), GS affects primarily the small intestinal mucosa (GS enteropathy [GSE] or celiac disease [CD]).[1,2] Symptoms include abdominal cramping, pain, and distention, as well as diarrhea, failure to thrive or weight loss, irritability, and weakness.[1,2] A significant proportion of children may have delayed onset of disease and may have minimal or unusual intestinal complaints, including recurrent abdominal pain, nausea, vomiting, bloating, and constipation, along with various extraintestinal manifestations, such as short stature, pubertal delay, and iron deficiency (CD with nonclassic symptoms).[2] GSE can occur in apparently healthy persons (silent CD) or later in life in persons with positive GS autoantibodies but a normal to minimally abnormal mucosa on intestinal biopsy (potential CD).[2] The prevalence of CD has been reported to vary from 1/99[4] to 1/200[1,5] in the general population; an Italian survey found an annual incidence of 0.11 to 0.17/1000.[6]

Numerous CD-associated extraintestinal conditions have been described, mostly in adults but also in children[1-3]; in these individuals, GS may pass unnoticed for a long period. These forms of GS have been interchangeably defined as atypical, cryptic, or occult GS.[1,3] Among the extraintestinal manifestations, a growing number of studies have reported a wide spectrum of neurologic conditions classically associated with GS.[7-17] The

AGA	Anti-gliadin antibody	GS	Gluten sensitivity
CD	Celiac disease	GSE	Gluten sensitivity enteropathy
EEG	Electroencephalography	HIE	Hypoxic-ischemic encephalopathy
ELISA	Enzyme-linked immunosorbent assay	tTG	Tissue transglutamine
EMA	Anti-endomysial antibody		
ESPGHAN	European Society for Pediatric Gastroenterology Hepatology and Nutrition		

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present study investigated the neurologic and psychiatric manifestations in a given population of children with GS and the prevalence of GS in a cohort of consecutive children with neurologic disorders of known and unknown cause.

METHODS

Subject Selection

The GS clinic at the Department of Pediatrics, University of Catania is the referral center for the town of Catania (which has 336,000 inhabitants, 98,000 of whom are children) and for patients with GS or GSE and their families who live in the province of Catania in eastern Sicily (which has an overall population of 967,000 of the 5.6 million inhabitants of Sicily), as well as others from other eastern (Siracusa and Ragusa) and central (Enna and Caltanissetta) provinces of Sicily.

Between January 1991 and December 2004, 1519 patients were evaluated at the GS clinic; of these, 1263 were diagnosed as having GS with or without associated GSE (346 males, 917 females; age range, 8 months to 69 years; median age, 9.6 years) and were regularly followed at the GS outpatient clinic. Three groups were excluded from the present study: (1) 127 adults (age > 18 years) (35 males, 92 females) with GS or GSE; (2) individuals referred to or coming from other eastern Sicilian provinces or from the province of Catania outside of the town of Catania, including 191 children (50 boys, 141 girls; age range, 9 months to 17 years; median age, 8.9 years); and (3) individuals affected by GS who were lost to follow-up, including 110 children (30 males, 80 females). The remaining 835 subjects (231 boys, 604 girls; age range, 9 months to 17 years; median age, 7.8 years) were representative of the GS population of the town of Catania; these figures closely matched (to 99.2%) the pediatric lists of GS subjects obtained from general practitioners and general pediatricians working in Catania. Of these 835 subjects, 667 were on a strict gluten-free diet, and 168 had poor diet compliance during the different phases of the study. Of the 667 subjects on a strict gluten-free diet, 45 (6.7%) had started the diet before age 2 years due to severe GSE; 55 (8.2%) had started the diet between age 2 and 6 years due to intermediate GSE phenotypes; 502 (75.2%) had started the diet between age 6 and 9 years due to failure to thrive, anaemia, or both; and 65 (9.7%) had been started the diet after age 9 years due to either mild GS symptoms or identification on GS screening.

The gluten-free diet regimens were monitored by the parents and/or guardians and checked at follow-up interviews every 6 to 9 months. The 835 subjects had been hospitalized at the time of diagnosis, carefully examined (general and neurologic examination), and investigated based on the results of the clinical evaluation. Routine screening included routine laboratory tests, heart and abdominal ultrasonography, and full ophthalmologic examination, including fundoscopy.

The University Pediatric Neurology Unit at our Department of Pediatrics is the primary referral center for all children with neurologic disorders in the town of Catania. The target population of this study consisted of 3 groups: children with neurologic dysfunction of unknown cause, children with known neurologic syndromes, and healthy controls.

Children with Neurologic Dysfunction of Unknown Cause

All consecutive children who were fully evaluated and found to have neurologic disorders of unknown cause (n = 90 per year) between 1998 and 2004 were screened for GS when they were seen in the unit. This group comprised 630 children with the following clinical features: developmental delay (n = 270), epilepsy (n = 180), mental retardation (n = 100), headache (n = 50), chorea (n = 12), ataxia (n = 10), and neuropathy (n = 8).

Children with Known Neurologic Syndromes

A group of 300 children with specific neurologic diagnoses were consecutively recruited and screened for GS. These children's diagnoses included neurofibromatosis type 1 (plus failure to thrive) (n = 54), neurofibromatosis type 2 (n = 24), tuberous sclerosis complex (n = 42), complex malformation syndromes (n = 23, including Sotos syndrome [n = 7], fragile X syndrome [n = 5], Rubinstein-Taybi syndrome [n = 3], Marfan syndrome [n = 3], Opitz-Kaveggia syndrome [n = 3], and Pallister-Killian syndrome [n = 2]), Rett syndrome (n = 22), brain malformation dysplasia (n = 22, including lissencephaly [n = 7], callosal agenesis with cyst [n = 5], cortical heterotopias [n = 4], double cortex [n = 4], and subependymal heterotopias [n = 2]), paraneoplastic neurologic syndromes (n = 21, including leukemia [n = 12], neuroblastoma [n = 5], and non-Hodgkin lymphomas [n = 4]), cerebellar degeneration (n = 20, including carbohydrate-deficient glycosylation syndromes [n = 18] and episodic ataxia type 2 [n = 2]), multiple sclerosis (n = 18, including relapsing-remitting [n = 16] and primary progressive [n = 2] forms), known leukodystrophies (n = 18, including Krabbe disease [n = 6], adrenoleukodystrophy [n = 4], metachromatic leukodystrophy [n = 4], Canavan disease [n = 2], and vanishing white matter disease [n = 2]), ataxia-telangiectasia (n = 17), congenital myasthenia syndromes (n = 10, with mutations of the epsilon subunit of the acethilcoline receptor), and congenital muscular dystrophies (n = 9, including muscle-eye-brain disease [n = 3] and Fukuyama disease [n = 6]).

In these children, the clinical, laboratory, neurophysiologic, neuropsychological, and imaging investigations done to exclude or include known neurologic conditions varied depending on the clinical indications. All patients included in the study were followed as outpatients unless specific medical conditions or disease complications necessitated hospitalization.

All of the children in the groups with neurologic dysfunction of unknown cause and known neurologic syndromes were tested for GS antibodies (see the Methods section) at the time of their first diagnostic workup—specifically, either during the acute phase of their disease (eg, epilepsy, headache,