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Review

Neuropsychiatric manifestations in celiac disease

Chiara Maria Trovato [a], Umberto Raucci [b], Francesco Valitutti [a], Monica Montuori [a], Maria Pia Villa [c], Salvatore Cucchiara [a], Pasquale Parisi [c,*]

[a] Maternal and Child Health Department, Pediatric Gastroenterology and Liver Unit, Sapienza - University of Rome, Italy
[b] Pediatric Emergency Department, "Bambino Gesù" Children's Hospital, IRCCS, Rome, Italy
[c] NESMOS Department, Faculty of Medicine and Psychology, Sapienza University, Sant'Andrea Hospital, Rome, Italy

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ABSTRACT

Celiac disease (CD) is a systemic, chronic immune-mediated disorder elicited by gluten and related prolamines in genetically susceptible subjects. Main manifestations of CD involve the digestive tract; however, a growing body of evidence supports the theory that symptoms may occur in every part of the body. It is known that some patients with CD can be asymptomatic, and additionally, the incidence of "nonclassical" CD with extraintestinal presentation is apparently increasing. We aimed to perform a thorough review of existing evidence for neurological manifestations of CD, providing an up-to-date description of prevalence and examining the pathogenetic mechanisms possibly involved.

Neurological presentations are rare in children but as many as 36% of adult patients present with neurological findings. With severe malnutrition after progression of CD, different vitamin deficiencies may develop. Such problems can in turn overlap with previous neurological abnormalities including ataxia, epilepsy, neuropathy, dementia, and cognitive disorders. Here, the most prevalent clinical manifestations in adults and children have been discussed in further detail.

Further research is needed to achieve a complete understanding of the nervous system involvement in CD, but clinicians should always remember that neurological and psychiatric symptoms might be part of the CD spectrum of manifestations.

1. Introduction

Celiac disease (CD) is a systemic, chronic immune-mediated disorder elicited by gluten and related prolamines in genetically susceptible individuals and characterized by the presence of a variable combination of gluten-dependent clinical manifestations, CD-specific antibodies, HLA-DQ2 or HLA-DQ8 haplotypes, and enteropathy, making it most common genetically based food intolerance in the world [1,2]. The prevalence of CD varies from 0.5%–1% in the general population to 4.5% among first degree relatives of patients affected with CD [3,4], and it is seemingly increasing over time [5,6]. Clinical presentation of CD can be extremely variable, ranging from silent to symptomatic to celiac crisis [7]. Nowadays, prevalence of the classic form of CD seems to be decreasing, while incidence of nonclassical CD with extraintestinal presentation is apparently increasing [8]. In literature, the rates of extraintestinal manifestation of CD are similar in adults and in children. Anemia, fatigue, headache, and psychiatric disorders are most commonly observed among adults; in children, short stature, fatigue, and headache are more represented [8]. Among extraintestinal symptoms, neurologic disorders, such as cerebellar ataxia, peripheral neuropathy, and epilepsy, have been recognized as both complications and initial manifestation of CD [9,10], and they have been described since 1966 [11]. Nevertheless, a wide range of neurological manifestations (such as migraine, epilepsy, encephalopathy, chorea, brain stem dysfunction, myelopathy, mononeuritis multiplex, and Guillain-Barré-like syndrome) could be considered as extraintestinal manifestations of CD [12]. Neurological presentations as the first signs of CD are rare in children but as many as 36% of adult patients present with neurological changes. With severe malnutrition after progression of CD, different vitamin deficiencies may develop. Such problems can in turn overlap with previous neurological abnormalities including ataxia, epilepsy, neuropathy, dementia, and cognitive disorders [13]. The first step for celiac diagnosis is searching for autoantibodies; IgA total and antitransglutaminase IgA

* Corresponding author at: Child Neurology, Pediatric Headache & Sleep Disorders Centre, NESMOS Department, Faculty of Medicine and Psychology, Sapienza University, Via Di Grottarossa, 1035–1039, 00189 Rome, Italy.
E-mail address: pasquale.parisi@uniroma1.it (P. Parisi).

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are mandatory for the screening. If the screening test is positive, the children should be referred to a gastroenterologist for a correct and definitive diagnosis of CD, based on current guidelines.

1.1. Prevalence

It is currently broadly believed that 5–6 times more patients present with nonclassical (atypical) or silent form than with the "classical" disease – a phenomenon described as the "CD-iceberg" in which only the "tip" of the iceberg has typical symptoms [7]. Neurological manifestations can thus appear at any time during the course of the disease – either before or after classical signs and symptoms, or even the first or the only symptom of CD [14].

Prevalence of neurological complications of CD in adults has been estimated higher than in children. In fact, neurological manifestations have been reported in approximately 6–10% of children with CD on the result of a systematic review and meta-analysis [15]. In literature, at the current state of knowledge, data about the prevalence of these complications are diverging: a 6.8% prevalence of neurological manifestations as initiating symptoms is reported [16]; an 11% of children had subclinical neurological abnormalities associated with CD based on other research [17]; it should also be specified that 13.5% of patients with CD had a neurological findings at the neurological evaluation [18]; quite different data have been shown by Zelnik, who described a prevalence of 51.4% of neurological disorder in patients with CD as assessed with a questionnaire [10].

2. Pathogenesis

The pathogenesis of neurological manifestations is unclear, but different types of mechanism have been suggested such as nutritional, immunological, toxic, and metabolic mechanisms and hyperhomocysteinemia [16]. Nutritional deficits, gluten toxicity, and gluten-related autoantibodies are involved in the pathogenesis of these symptoms. Malabsorption and nutritional deficiencies (especially of vitamin B6 and tryptophan) have been described [19]. Deficit of vitamin B12 seems responsible for myelopathy and neuropathy, vitamin D malabsorption for myopathy, and vitamin E deficiency for cerebellar ataxia and myopathy [12]. Malabsorption of vitamin B likely exposes patients with CD to hyperhomocysteinemia, and increased serum homocysteine has been described as a possible cause of epilepsy and migraine [20]. By damaging the blood–brain barrier, hyperhomocysteinemia might cause neuronal exposure with neuroirritative metabolites [21]. A possible role of free radical accumulation with oxidative stress and a role of toxin deposition as triggers of seizure have been hypothesized in patients with CD [16]. Moreover, CD may overlap with other autoimmune diseases such as type 1 diabetes, autoimmune thyroid disease, Addison's disease, and autoimmune atrophic gastritis [22]. Patients with CD frequently develop antibodies against antigens related to the endocrine organs [23], and in the same way, some authors described autoantibodies acting as possible "triggers" of neurological manifestations [21,23]. The presence of autoantibodies against neuronal cells, such as antitissue-transglutaminase type 6, GAD65, and VGKC-complex IgG, could explain the pathogenesis of neurological manifestations, possibly through a molecular mimesis mechanism [24]. A high prevalence of antineuronal antibodies against central nervous system in patients with CD with neurological manifestations is reported [25]; these autoantibodies might suggest an immune-mediated pathogenesis leading to central neural impairment as well as gut dysfunction. The same type of autoantibodies was previously found by Volta et al. in 2002; the authors reported the disappearance of these autoantibodies after 1 year of a strict gluten-free diet (GFD) [26]. On the other hand, in 2006, Tursi et al. showed the persistence of neurological damage and autoantibodies in well-treated CD despite GFD and despite a good histological response, hypothesizing that an important role could be played by the duration of gluten exposure [27]. A different type of autoantibodies directed against Purkinje cells was found in sera of patients with gluten ataxia (GA) [28]. The role of autoantibodies in neurological manifestation is still unclear. In conclusion, the risk for developing neurological manifestation, as for other autoimmune disorders [29], seems higher in case of long-standing gluten exposure. This could also underlay the different prevalence of neurological disturbances in adults and in children [30].

3. Clinical manifestation

Celiac disease resembles an iceberg phenomenon. Few patients present with classical signs and symptoms primarily to CD or secondary to vitamin deficiencies and nutrient malabsorption. A bigger group of individuals have some manifestations that are not related to gastrointestinal malabsorption, e.g., osteopenia, anemia, and neurologic complications; this type of disease is called atypical CD. Most patients are asymptomatic and diagnosed by serologic investigation and histopathological studies; this type of disease is referred to as silent CD [13].

Although gluten sensitivity is classically a disease of infants, CD often presents in later, especially in the second and fifth, decades of life. Consequently, well-known features of a child with life threatening malabsorption is replaced by an atypical or silent CD in adults [31]. Neurological presentations are rare in children but as many as 36% of adult patients present with neurological changes [13]. Several neurologic and psychiatric manifestations are significantly associated with CD in pediatrics.

4. Neurological manifestations

Children with CD are at risk of developing neurological complications, but the risk is lower than in adulthood. The discrepancy might be due to short disease duration, early elimination of gluten from the diet, stricter adherence to diet, or different susceptibility to immune-mediated disorders [15].

Several neurological manifestations are significantly associated with CD in the pediatric population. The most common is headache, that is present in up to one-fifth of the cases. Rarer conditions in the pediatric population are ataxia, neuropathy, and brain white matter lesions [15,32]. The link between epilepsy and CD remains still uncertain. The most common seizure patterns are the complex partial, followed by tonic–clonic seizures.

4.1. "Gluten ataxia"

Gluten ataxia is one of the most common neurological manifestations of gluten-related disorders, and it has been firstly reported in 1966 [33]. Recently, a consensus paper reported that GA had a prevalence of 15% among all ataxias and 41% among idiopathic sporadic ataxias [34].

Dysarthria, dysphonia, pyramidal signs, and eye and gaze movement disorders are characteristic presentations; these symptoms, however, result indistinguishable from other type of cerebellum ataxia. Ataxia related to CD is not often associated with typical gastrointestinal symptoms or malabsorption signs [3]. Ataxia in CD often lacks particular clinical features of distinguishable types of ataxia (cerebellar and sensory ataxias) [35]. However, in many patients with ataxia, cerebellar involvement may occur in the presence of low level of vitamin E [36]. Most patients will either stabilize or improve with strict adherence to GFD, depending on the duration of the ataxia prior to the treatment. Up to 60% of patients with GA have evidence on MR imaging of cerebellar atrophy [37]; gliosis, Purkinje cell depletion, atrophy, and degeneration of posterior column of the spinal cord have been described in postmortem examination [11]. If strict GFD does not improve symptoms of ataxia, intravenous immunoglobulins seem to provide beneficial effects. The prevalence of this condition is very different in adults and children, as it might reach up to 40% in adults compared with low or null

prevalence of cerebellar dysfunction in children [15]. Ataxia may be developed as a pancerebellar syndrome because of presentation of enteropathy associated T cell lymphoma and lymphomatous metastases to the cerebellum. This diagnosis should be kept in mind for patients with CD-related enteropathies before relating cerebellar findings to different vitamin or other nutritional deficiencies or an associated autoimmune mechanism [38].

4.2. Epilepsy

The link between epilepsy and CD remains still uncertain and debated; nevertheless, the association between CD and epilepsy is described, and the risk of epilepsy is increased in both children and adults [39–42]. The majority of patients had complex partial seizures referable to the occipital or temporal lobes; however, secondarily generalized seizures, or other seizure types and episodic headaches also were reported [43,44]. In children, the prevalence is varied, ranging from 0% [17] to 7.2% [10], but a definite esteem depends on the chosen criteria, as febrile convulsions have been often included. In a group of children with atypical CD, a prevalence of 3.41% was reported [16]. A pediatric meta-analysis found a 2.1-fold increased risk of epilepsy in pediatric patients with CD [15]. In 2012, Ludvigsson et al. calculated hazard ratios (HRs) for epilepsy in patients with CD and concluded that CD was associated with a 1.43-fold increased risk of epilepsy, independent of temporality. The risk for epilepsy was increased both before and after CD diagnosis, and it suggests common underlying etiology or predisposition as a cause of epilepsy, rather than CD itself [45]. The effect of GFD on epilepsy control in CD has been variable. In most patients, the beneficial effects of diet have been reported as better seizure control and a decrease in antiepileptic medication, but not as the complete resolution of seizures [46–49]. The first report of the triad "Celiac disease, epilepsy, and cerebral calcification" (CEC) probably was described from Sammaritano et al. in 1985 [50]. The first study that clearly suggested the specific CEC syndrome was published by Gobbi et al. in an Italian multicenter study in 1992; they firstly described 29 patients (age range: 4.6–30.7) with these particular conditions [46]. These authors concluded that CD should be included in differential diagnosis in all case of epilepsy and cerebral calcifications of unexplained origin. Then further patients with CEC were published in Italy (age range: 6–23), including one case report of partial epilepsy [47,51,52], and in other countries in both pediatric [44,53] and young adult populations [54]. This syndrome is present in 0.7% of children analyzed in a pediatric meta-analysis [15]. Some studies suggest that cerebral calcification might develop only later in life and an early treatment of CD can reduce the risk of developing calcifications [15]. It is important to stress that prevalence of CD increased among patients with epilepsy; the prevalence of CD was 2.3 higher in patients with epilepsy than in controls [55]. For these reasons, patients with epilepsy should be screened for CD [56].

4.3. Headache

Some studies describe the association between CD and headache, both in adult and children [10,57–59]. The prevalence of headache in adults with CD seems to be higher than in controls (46% vs 29%) [57]. Serratrice et al., in 1998, described headache as a symptom of CD in its classic, atypical, and silent form that responds to GFD [60]. In 2009, Lionetti et al. showed a high prevalence of headaches (24.8%) in a pediatric population and demonstrated that headaches significantly improved in 77.3% of patients with CD following GFD [61]; similar results were previously observed [10,17]. A pediatric meta-analysis [15] showed that the relative risk (RR) of patients with CD developing headache is 3.2 (95% confidence interval [CI]: 2.2–4.7), the odds ratio (OR) is 4.0 (95% CI: 2.6–6.1; $p < 0.001$; $I^2 < 27.6\%$), and the risk difference (RD) is 0.08 (95% CI: 0.06–0.11; $p < 0.001$; $I^2 = 99.7\%$), indicating that children with CD may be at higher risk of headache compared with controls. Similar to epilepsy, CD prevalence is doubled in patients with chronic headache. Screening for CD could be advised as part of the diagnostic workup in these pediatric patients, particularly among nonresponders to pharmacological treatment [62].

4.4. Peripheral neuropathy

Peripheral neuropathy is the second most common neurological manifestation in adults with CD and has been found in up to 49% of patients with CD [57]. Neuropathy is described as chronic distal, symmetric, and predominantly sensory, in the form of distal sensory loss, paresthesias, and imbalance [18]; however, mere motor neuropathy, mononeuritis multiplex, Guillain-Barré-like syndrome, and autonomic have been described [63–66]. Motor weakness is rare and confined to the ankles [11]. The predominant manifestation of peripheral neuropathy in physical examination of patients with CD is sensory neuropathy with variable involvement of large and small fibers [66,67]. Electrophysiologic studies describe a large spectrum of manifestation in patients with CD; in fact, some patients with CD do not show electric sign of neuropathy, and in other, a mixed sensorimotor axonal peripheral neuropathy has been found [63–66]. In 2005, Tursi et al. described the presence of antineuronal antibodies (anti-GM1 antibodies) in adults, but the symptoms did not disappear in spite of antibodies disappearance during follow-up [27]. The effect of GFD is unclear; some authors described the diet as effective [63,68], while others indicated the persistence and progression of neuropathy despite an adequate GFD [69–71]. Only two studies investigated the prevalence of peripheral neuropathy in children with different results: Cakir et al. [17] described a prevalence of 4.7% while Ruggieri et al. [30] found only one female out of 835 children investigated.

4.5. Rare neurological manifestations of CD

In literature, case reports snapshot different types of neurological manifestation in CD. A case of a 14-year-old girl with constipation and pseudotumor cerebri (headache, papilledema with lack of structural defect) was described in 2015. For severe constipation, she was diagnosed as having CD. The patients started GFD leading to resolution of both gastrointestinal symptoms and symptoms of pseudotumor cerebri [72]. In 2015, Plant et al. reported case of a patient with CD and cerebral occipital calcification who showed a progressive and seemingly selective failure to recognize visual stimuli [73]. In 2016, a case report portrayed a 17-month-old girl with CD and a transverse myelitis diagnosed with MR. After the start of both GFD and methylprednisolone, she recovered completely [74]. Cases of transverse myelitis have been previous described in adults [75]. In 2006, Belgian authors reported the case of a 2-year-old male who presented with opsoclonus-myoclonus syndrome including action myoclonus, palpebral flutter, opsoclonus, and ataxia. Brain MR imaging was normal on two occasions, and oligoclonal bands were present in the cerebrospinal fluid. Serum screening for CD was positive, and duodenal biopsy confirmed the diagnosis of CD [76]. Moreover, a case report describing a child presenting with recurrent transient hemiplegia was published in 2004: CD serology was strongly positive, and a duodenal biopsy confirmed the disease [77].

5. Neurological investigation

5.1. EEG findings

The spectrum of electroencephalography (EEG) features associated with CD is rather wide; focal activity in terms of unilateral or bilateral spike or slow waves, mainly localized in the occipital regions, has been reported in most of the wakefulness EEG studies [51,55,78–80]. In childhood, epilepsy is one of the most frequent manifestations of neurological complication [15]. Only one study [59] has investigated the prevalence of neuronal hyperexcitability and subclinical EEG abnormalities in asymptomatic children with newly diagnosed CD. In this study,

the EEG examinations revealed abnormal findings, such as focal or generalized sharps and/or spikes and spike-waves in 47.4% without clear recognizable clinical manifestations. Given these premises, Pennisi et al. claimed "hyperexcitable brain" in CD [14].

5.2. Electrophysiological tests

In adult, patients with CD have an increased frequency of chronic axonal neuropathy, even when adhering to a long-term strict GFD. Early detection of CD might prevent the development of manifest neuropathy. Subclinical peripheral neuropathy in patients with CD without electrophysiological changes is demonstrated by lower pain threshold and reduced heat and touch sensations; 23.1% of patients with CD showed findings of chronic axonal neuropathy in quantitative needle EMG; in addition, two CD showed findings suggestive for myopathy; an increased occurrence of axonal neuropathy was observed in well-treated CD, and this further indicates that neurological manifestations occur even in patients without overt malabsorption [71].

Involvement of the peripheral nervous system in children with CD is not frequent (see dedicated paragraph).

In asymptomatic cases with CD, electrophysiological studies are not necessary. In fact, a recent study on 167 asymptomatic patients as well as the predisposing factors for polyneuropathy as well as 100 control cases were tested electrophysiologically for peripheral nervous system diseases. Motor nerve conduction studies, including F-waves, were performed for the median, ulnar, peroneal, and tibial nerves; and sensory nerve conduction studies were performed for the median, ulnar, and sural nerves with H reflex of the soleus muscle unilaterally. Evidence for subclinical neuropathy was not determined with electrophysiological studies [18].

5.3. Imaging

Patients with CD referred for neurological consultation have significant abnormalities on MR imaging of the brain and the cerebellum. In particular, patients with CD have significantly reduced gray matter volume in multiple brain regions, including cerebellum, and a higher proportion of cerebral white matter abnormalities, especially in patients with headache [81]. Previously, unilateral and bilateral focal T2 hyperintense white matter lesions were found [82]. Brain images play an essential role in the diagnosis of a CEC syndrome (celiac disease, epilepsy, and bilateral occipital calcification) [46,83]. The CEC syndrome is a focal or complex partial type of epilepsy usually originating from the occipital lobe. TC and MR findings show bilateral cortical and subcortical occipital calcification, absence of lobar or hemispheric atrophy, and absence of contrast enhancement not associated with atrophy or vascular anomalies [51]. By using radiograph spectroscopy, calcium and silica were present in these calcifications [84].

6. Psychiatric and psychological manifestations of CD

Psychiatric disorders have been reported as a complication of CD in many patients, and several studies showed symptom improvement after starting GFD. Psychiatric symptoms usually described in patients with CD include depressive symptoms, apathy, excessive anxiety, irritability, eating disorders, and attention-deficit/hyperactivity disorders (ADHD) [85]. One study reported that patients with CD were significantly more likely to have state anxiety compared with controls [86]. A meta-analysis on anxiety and depression in CD found that depression is more common and more severe in adults with CD compared with healthy controls [87]. Social phobia seems to be increased as well in patients with CD [88], and a higher lifetime prevalence of panic disorders has been found [89]. Campagna et al. reported that patients with CD showed significantly higher scores of anxiety, harm avoidance, separation panic, and somatic complaints, even after the introduction of GFD [90]. The introduction of GFD induces a high level of anxiety, which may be have different features according to gender, resulting in depression in female and aggressive behavior and irritability in males. The association between schizophrenia and CD is known since 1950s; symptoms of schizophrenia seem to improve by adherence to a strict GFD. There is no definite evidence suggesting whether CD occurs before the onset of schizophrenia or vice versa [91,92]. A recent Sweden multicentric study shows that there is a higher risk to develop psychiatric disorders in children as well. In fact, compared with the general population, children with CD had a 1.4-fold greater risk of future psychiatric disorders. Childhood CD was identified as a risk factor for mood disorders, anxiety disorders, eating disorders, behavioral disorders, ADHD, ASD, and intellectual disability [93]. The TEDDY Study Group reported that CD autoimmunity is associated with increased reports of child depression and anxiety, aggressive behavior, and sleep problems when mothers are unaware of their children CD autoimmunity status [94]. In a recent comprehensive review, it was ascertained the presence of

Table 1
Prevalence and responses to GDF diet of neuropsychiatric manifestations in CD.

Neurological manifestation	Symptoms	Prevalence	Other information	Effect of GFD
Gluten ataxia (GA)	Dysarthria, dysphonia, pyramidal signs, eye and gaze movement disorders	15% among all ataxias; 41% among idiopathic sporadic ataxias	Seldom associated with typical gastrointestinal symptoms	Improvement or stabilization for most patients
Epilepsy	Complex partial seizure, secondarily generalized seizures	Ranging between 0 and 7.2%	Increased risk of developing epilepsy	Variable effect; improved seizure control and decreased antiepileptic medications
CEC syndrome	Celiac disease, epilepsy, and cerebral calcification	0.7% of pediatric patients with CD	Focal or complex partial type of epilepsy usually originating from the occipital lobe. TC and MR: bilateral cortical and subcortical occipital calcification, absence of lobar or hemispheric atrophy, and absence of contrast enhancement	Reduced risk of calcification development
Headache	Headache, migraine	46% of adult with CD; 24.8% in pediatric population	3.2 RR of developing headache for patients with CD	Headache improvement (77.3%)
Peripheral neuropathy	Chronic distal neuropathy, symmetric and predominantly sensory neuropathy; distal sensory loss, paresthesias, motor neuropathy, mononeuritis multiplex, Guillain-Barré-like syndrome, and autonomic neuropathy	49% of adult patient with CD; 4.7% in children with CD	Variable involvement of large and small fibers; presence of antineuronal antibodies (anti-GM1 antibodies) in adults	Inconclusive evidence: diet is described as effective, while others indicated the persistence and progression of neuropathy despite an adequate GFD.

an association between CD and psychiatric disorders with varying grades of evidence: there is enough evidence supporting an association of CD with depression and, to a lesser extent, with eating disorders; an association between CD and panic disorder, autism, and ADHD is possible but the evidences are limited; data regarding the association of CD with schizophrenia or other anxiety disorders are conflicting [95].

7. Conclusions

Based on current evidence, patients with CD have an increased risk to develop neurological and psychiatric disorders. Neurological disorders in CD are summarized in Table 1 and should be always considered as a red flag for undiagnosed CD (Table 1). At present, prevalence of these disturbs in adult and in children is not clear, and further research is needed to understand their pathogenesis. Gluten-free diet seems to have beneficial effects in neurological complaints, epileptic discharges, and neuropsychiatric symptoms, as it can improve these manifestations. Neurological involvement in CD is a widespread phenomenon, and more accurate testing should be performed in these patients in order to reach a correct diagnosis. Routine surveillance of potential neurological and psychiatric manifestations should be carried out by gastroenterologists and other healthcare professional involved both at diagnosis and all time of follow-up in the management of patients with CD. Careful assessment is needed in order to refer the child or adult to the neurologic or psychiatric departments, as appropriate, to reach a correct diagnosis early with relative appropriate treatment. In the same way, the neurologist should suspect CD in patients with the aforementioned neurological symptoms. Considering the known increased RR of epilepsy and headache in patients with CD (and vice versa), these patients should undergo CD screening at the moment of the diagnosis and during follow-up. In our opinion, before jumping to rushed conclusions, a complete diagnostic workout should be performed by a specialist in CD in order to suggest a GFD only when necessary.

Founding source

None.

Declaration of Competing Interest

The authors declare no conflict of interest or financial disclosures concerning the materials or methods used in this study or the findings specified in this article.

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