SUBCLINICAL AXONAL NEUROPATHY AT ONSET OF CELIAC DISEASE IN A PEDIATRIC COHORT

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[Neuropatia assonale subclinica in una piccolo coorte pediatrica con recente diagnosi di celiachia]

ABSTRACT

Celiac disease (CD) is a multifactorial enteropathy induced by the ingestion of gluten in susceptible individuals. It’s widely accepted that CD is an immune-mediated enteropathy and clinical manifestations range from typical signs or symptoms of intestinal malabsorption to atypical cases with scarce gastro-intestinal symptoms and extra-intestinal manifestations. Several neurological syndromes have been associated to CD and include epilepsy, myoclonus, ataxia, internuclear ophthalmoplegia, multifocal leukoencephalopathy and peripheral neuropathies of axonal and demyelinating type. In this small case series, electromyography and the study of nerve conduction were performed in 10 young children at first diagnosis of CD without any neurologic sign or symptom. The presence of mild axonal polyneuropathy was revealed in 6 patients, especially involving motor fibers and showing great affinity to peroneal fibers.

Key words: Celiac disease (CD), nerve conduction study, axonal polyneuropathy.

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Introduction

Celiac disease (CD) is an enteropathy triggered by an immune reaction to gluten, a protein found in wheat, rye and barley and usually occurs in genetically susceptible individuals. Clinical spectrum is wide, ranging from typical gastrointestinal manifestations to absent or unusual manifestations. CD can present at any age but in childhood, it usually occurs with typical symptoms and signs(1).

The prevalence is high in the general population (0.7-2%), and between 0.4 and 1.3% in the pediatric population(2). Genetic predisposition is mainly related to the expression of genes located on the HLA system, namely the HLA-DQ2 and DQ8 genotypes, found in 98% of patients. Moreover, Down syndrome, Turner syndrome, Williams syndrome and IgA deficiency are known to be genetic disorders associated to CD. Clinical presentation of CD can be typical, atypical, silent and potential. In classical, atypical and silent CD, histology shows a fully expressed enteropathy. Typical CD often presents with abdominal distension, anorexia, chronic diarrhea, muscle wasting and coeliac crisis. Non-classic symptoms include extra-intestinal manifestations such as arthritis, aphthous stomatitis, dermatitis herpetiformis, iron-deficient anemia, growth and pubertal delay.

Serological screening can reveal silent CD whilst potential cases are those in which serology is positive but intestinal damage occurs later in life. Since the immune-mediated nature of the disease, CD is as well as associated to autoimmune diseases, including type 1 diabetes, thyroiditis and Sjogren’s syndrome.

Neurologic presentation of CD comprises peripheral neuropathy, cerebellar ataxia, myelopathy, myopathy, brains tem encephalitis, epilepsy,
headache and autism\(^{(3)}\) and in most of cases, classical symptoms precede neurological manifestations. Vitamin B12 and vitamin E deficiency, vitamin D malabsorption and immune-mediate mechanisms are likely to play a crucial role in the pathogenesis of neurological complications in CD. As for peripheral neuropathy, in a recent study, more than 49% of CD patients presented peripheral neuropathy\(^{(4)}\). In adults, peripheral neuropathy is often chronic, symmetric and predominantly sensory\(^{(3)}\) but Guillain-Barré-like syndrome, pure motor neuropathy and mononeuritis multiplex have also been described\(^{(5)}\). Cakir et al. (2007) reported an incidence of 7.4% of neuropathy with axonal motor and sensory both involvement and pure sensory polyneuropathy\(^{(6)}\). According to several studies, gluten-free diet can remit polyneuropathy\(^{(7,8,9)}\). In this case series, we have evaluated 10 young patients at CD onset to detect any peripheral neuropathy by using electromyography and study of nerve conduction.

### Materials and methods

**Case series**

We selected 10 patients (4 M, 6 F; mean age ± SD=9.5±2.4 years) from the Pediatric Department of the Pediatric Hospital of Palermo who had a first diagnosis of coeliac disease (CD). The onset of CD consisted of classical symptoms such as abdominal distension, chronic or recurrent diarrhea, anorexia, failure to thrive or weight loss, irritability and muscle wasting in 2 patients, atypical symptoms such as arthritis, aphthous stomatitis, constipation, dental enamel defects, iron-deficient anemia, recurrent abdominal pain occurred in 4 patients, 4 patients were asymptomatic. The diagnosis of CD was made according to the New Guidelines for the Diagnosis of Celiac Disease proposed by the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) in 2012\(^{(10)}\). No patient suffered from any disease except for CD.

No patient could complain of any strength or sensitive deficiency. All patients had been evaluated at the general outpatient Neurology outpatient Department to which they were referred by their general practitioners. Neurological examination was normal in every patient. Standard techniques for electrophysiological examination were used. Skin temperature was maintained at between 32°C and 35°C. The electrophysiological studies included motor conduction velocity in right or left ulnar and/or median, posterior tibial and peroneal nerves bilaterally, sensory conduction velocity in ulnar, sural and/or superficial peroneal nerves bilaterally. Electomyography (EMG) of distal arm and leg muscles was also carried out.

### Results

Motor Nerve conduction study is summarized in table 1. Motor and sensory conduction velocities were both normal.

In our patients:

- 6 patients presented reduced amplitude of the compound Motor Action Potential or cMAP (less than 2 mV);
- Only one patient showed low amplitude of Sensory Action Potential or SAP.

Low amplitude cMAP (less than 2 mV) was found by stimulation of peroneal nerves in 6 patients, by stimulation of tibial nerves in 2 patients and by stimulation of left median nerve in 3 patients (Figure 1-2). F-wave latency was increased in low limbs whereas it was normal in upper limbs in every patients. EMG was normal in every patient.

HLA haplotype was determined for diagnosis: HLA DQ2-DR7 (n=4), DQ2-DR3 (n=3), DQ8-DR4 (n=1). No relation was found between nerve conduction findings and HLA haplotype whilst HLA haplotype distribution reproduced the frequency of them in CD.

### Discussion

Neurological complications of coeliac disease (CD) were firstly described by Cooke and Smith in 1966\(^{(11)}\): the authors reported cases of gait ataxia and peripheral neuropathy in CD patients. Since then, several studies have been reporting on different neurological conditions associated with CD although the exact prevalence of neurological disorders in CD is not known yet.

According to Finelli et al.\(^{(12)}\), the estimated prevalence of neurological disorders in gluten sensitivity amounts about 10%. Depression, migraine and epilepsy are the commonest neurological conditions related to CD\(^{(13)}\). Neurological conditions associated with CD are usually gait ataxia, epilepsy and peripheral neuropathy. Nutritional deficiencies, autoimmunity and inflammatory processes are probably the most important concurrent factors in aetiology of neurological complications.
The role of nutritional deficiencies deals with hypocalcemia referring to psychiatric features and myopathy, folic acid deficiency related to epilepsy and cerebral calcifications, vitamin B12 deficit linked to peripheral neuropathies and myelopathy occurring in CD patients.

In adults, involvement of peripheral nervous system has been systematically attributed to chronic, symmetric and predominantly sensory neuropathy\(^4\),\(^14\), Guillain-Barré-like syndrome, pure motor neuropathy and mononeuritis multiplex\(^6\). Cakir et al. (2007) reported an incidence of 7.4% of neuropathy with both axonal motor and sensory involvement and pure sensory polyneuropathy in children suffering from CD\(^7\). In one study, antibodies antigangliosides have been found in 65% with CD and neuropathy\(^15\). Furthermore, axonal polyneuropathies of unknown cause have been related to antigliadin antibodies in 34% of cases\(^16\). According to several studies, gluten-free diet (GFD) can remit polyneuropathy\(^8\).

In our study, we investigated the existence of subclinical neuropathy in 10 young patients with recent diagnosis of gluten enteropathy. EMG and the study of nerve conduction allowed us to detect mild reduction of compound motor action potential (cMAP) in 60% of cases, revealing a mild motor axonal polyneuropathy. According to our results, neuropathy associated with CD onset is more often axonal than demyelinating. Moreover, peroneal nerve is likely to be more affected than other nerves.

Table 1: Motor nerve conduction study in our cohort.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Left median nerve (digit II-wrist)</th>
<th>Right peroneal nerve (EDB)</th>
<th>Left peroneal nerve (EDB)</th>
<th>Right peroneal nerve</th>
<th>Left tibial nerve</th>
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<tbody>
<tr>
<td></td>
<td>Motor conduction velocity (msec)</td>
<td>Latency (msec) at the ankle</td>
<td>Amplitude (mV)</td>
<td>Motor conduction velocity (msec)</td>
<td>Latency (msec) at the ankle</td>
</tr>
<tr>
<td>1/F</td>
<td>66</td>
<td>2.9</td>
<td>5.4</td>
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<td>5.5</td>
</tr>
<tr>
<td>2/F</td>
<td>60</td>
<td>2.75</td>
<td>1.3</td>
<td>54</td>
<td>3.65</td>
</tr>
<tr>
<td>3/F</td>
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<td>3.3</td>
<td>7.5</td>
<td>54</td>
<td>3.3</td>
</tr>
<tr>
<td>4/F</td>
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<td>2.05</td>
<td>6.7</td>
<td>60</td>
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</tr>
<tr>
<td>5/F</td>
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<td>3</td>
<td>4</td>
<td>56</td>
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<tr>
<td>6/F</td>
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<td>55</td>
<td>3.3</td>
</tr>
<tr>
<td>7/F</td>
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<td>3</td>
<td>1.9</td>
<td>47</td>
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<tr>
<td>8/F</td>
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<tr>
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<tr>
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<td>2.25</td>
<td>5.2</td>
<td>60</td>
<td>3.55</td>
</tr>
</tbody>
</table>

Figure 1: Amplitude of cMAP in our patients.

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Figure 2: Amplitude of cMAP in different nerves in exam.

This preliminary study allowed us to find out that neuropathy is probably the most frequent neurological complication in pediatric CD. Despite the small size of our cohort, our results suggest that celiac patients should undergo a neurophysiological screening at onset and conversely, differential diagnosis of polyneuropathies should also include celiac disease.

References

3) Bushara KO, Neurologic presentation of celiac disease.


