Chapter 37

Neurological complications associated with coeliac disease: a personal study

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Introduction

Coeeliac disease is a malabsorption syndrome characterized by chronic gluten intolerance. Although its aetiology is unknown, an immunologic mechanism seems to be prominent. Numerous neurological and psychiatric disorders can be related to coeliac disease ranging from 10 to 30 per cent of all cases, depending upon the various case histories. The more frequent complications are epilepsy, mental retardation, schizophrenia, organic dementia, cerebellar disorders, myopathy and peripheral neuropathy. Over the last ten years, numerous cases have been reported, mostly in Italy, of coeliac patients affected by epilepsy having biopsiopathological cerebral calcifications, to the extent that a specific syndrome (CEC) has been identified and its clinical, electroencephalographic and neuroradiological characteristics defined (Fois et al., 1994; Gobbi et al., 1992; Molteni et al., 1988; Piattella et al., 1986; Piantella et al., 1987; Piantella et al., 1987; Piantella et al., 1990; Piantella et al., 1993; Sammaritano, 1985; Sammaritano et al., 1988; Zamboni et al., 1989).

Materials and methods

Data are reported regarding the neurological complications observed during the course of coeliac disease in 58 patients (15 M, 43 F), mean age 12.5 years, admitted to the Pediatric Neuropsychiatry Division and to the Medicine Division of the Regional Paediatric Hospital of Ancona. The diagnosis of coeliac disease was defined according to the criteria of either ESPGAN or the Paediatric Gastroenterology Group (1987). Coeliac disease was subdivided according to initial symptoms and the results of laboratory investigation into three categories: typical, atypical or latent. At diagnosis, the age of the patients was less than 6 years in 35 cases, between 6 and 12 in 10, and over 12 years in the remaining 13. All patients underwent dietary therapy and were periodically checked both from a clinical standpoint as well as with biochemical tests (AGA, antidiomysial antibodies,
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nutritional indices, complete haematological profile, etc.). Furthermore, positive anamnestic factors for headaches, convulsions, behavioural and psychic disorders and peripheral nervous system disorders specifically questioned. All patients underwent a neurological examination and EEG. In patients with neurological symptoms and/or altered EEG, the neurodiagnostic investigation was followed by neuroradiological (CT, MRI, SPECT), and neurophysiological (EP, EMG, MCV, SCV) examinations and psychodiagnostic evaluation.

Results

The more frequently observed neurological disorders were:

- Cerebral calcifications + epilepsy – 5
- Epilepsy without calcifications – 1
- Acute cerebral ischaemia – 1
- Migraine headaches – 4
- Cerebral neoplasia (with epilepsy) – 2
- Febrile convulsions – 3
- Isolated EEG alterations – 3
- Psychiatric disorders – 2

Cerebral calcifications – epilepsy – coeliac disease

From 1983 onwards, there have been ever-increasing reports of Sturge-Weber-like bioccipital cerebral calcifications in patients affected by epilepsy and other neurological disorders; some of these patients were also shown to have coeliac disease. Therefore, an aetio-pathogenic correlation has been suggested between the intestinal pathology and the cerebral parenchymal alterations found on neuroradiological examination. The pathogenesis of the calcified lesions and, more generally, of the neuropathological lesions found in patients with coeliac disease (gliosis, focal neuronal loss, chromatolysis, axonal damage, demyelination), is still unknown although various mechanisms have been invoked:

- Folic acid deficiency with consequent mineralizing microangiopathy and alteration of the normal myelination process (Byle et al., 1993; Fois et al., 1994; Garwicz & Mortensson, 1976; Pantella et al., 1987; Pantella, 1990; Sammartano et al., 1988);
- Vitamins and oligoelement deficiency, particularly selenium and vitamin E (Gregori et al., 1988; Ward et al., 1985);
- Mechanisms of an immunological type causing repeated vasculitises with consequent damage to the surrounding cerebral parenchyma. The chronic hyperperfusion and successive calcium and, perhaps, silicon deposits would represent the eventual evolution of the disease (Fois et al., 1994; Gobbi et al., 1992). The anatomico-pathological alterations seen in these rare cases where biopsy of the calcific lesions has been carried out show vascular anomalies (intimal fibrosis, pial angiomatisms, microcalcifications) similar to, but not identical to, those found in Sturge-Weber disease (Byle et al., 1993).

In recent years, five subjects of paediatric age affected by epilepsy, endocranial calcifications and coeliac disease were identified at the Pediatric Neuropsychiatry Division of the Regional Paediatric Hospital of Ancona; in particular, all cases had an atypical form of coeliac disease in that no intestinal symptoms were readily apparent, but rather the syndrome was manifested by low stature, constipation, pubertal retardation and anaemia.

The five patients (3 F, 2 M), ranging from 6 to 15 years of age, were admitted for observation due to epileptic syndromes of varying seriousness. In particular, two of the subjects had rare seizures at the outset, and these were partial and secondarily generalized, associated with slow EEG anomalies.
and centro-posterior foci; the evolution of the epileptic symptoms was favourable in both cases, entirely independent of dietary therapy.

The other three patients presented a clinical-EEG picture characteristic of the CEC syndrome recently identified and amply described in the literature (drug-resistant partial epilepsy with early onset polymorphic seizures evolving in phases, EEG alterations characterized by biocipital focal anomalies suppressed by eye opening, psychoneurological regression). Its subsequent clinical evolution over a long-term follow-up (in some cases more than 10 years) has shown persistence of the drug-resistant epilepsy and psychic regression in two cases; in the third case, the seizures have disappeared. EEG has normalized, and psychoneurological capabilities have improved, and antiepileptic therapy could be discontinued. In this patient, the seizures were already under control by antiepileptic therapy at the time dietary therapy was initiated. The parenchymal structural alterations persisted without change over the entire period of observation. One year after therapy was suspended, the patient developed insulin-dependent diabetes.

The diagnostic investigations showed the following:

- Anti-gliadin antibodies (AGA) and jejunal biopsy compatible in all cases with the presence of celiac disease;
- Low folate in four of the five cases;
- HLA: positive for haploidy DR3 and DQ2W2 in all patients;
- Constantly abnormal EEG with, in three cases occipital spike-waves of large amplitude reacting to opening of the eyes, with important secondary diffusion during sleep (Figs. 1-3);
- Cerebral CT with biocipital multiple hemispheric intraparenchymal calcifications (Fig. 3);
- Cerebral MRI: negative in all cases but one, in which a void signal compatible with calcification was seen in bispial-occipital areas (Fig. 4);

*Fig. 1. EEG (wakefulness): Slow spike-waves over both occipital regions suppressed by eye opening.*
Fig. 2. EEG (nonREM sleep): Continuous spikes and spike-wave discharges in both parietal-occipital areas with a tendency to diffuse.

Fig. 3. Cranial, CT: Bilateral cortical-subcortical occipital curvilinear symmetrical calcifications.
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Fig. 4. Magnetic resonance imaging (MRI): Areas of reduced signal in the parieto-occipital regions compatible with a suppression of calcifications.

- SPECT: reduced radioactivity bilaterally in parieto-occipital areas in one patient.
- Evoked potentials (VEPs, SEPs, BAPs): normal cortical responses in all subjects except one in whom pattern stimulation resulted in a lengthening of the P100 latency.
- EEG = MCv = SCV: normal in all.

These findings may lead to the following deductions:

- The cerebral calcification and epilepsy are almost certainly correlated etiologically to cortic disease even though the pathogenic mechanism is not entirely clear. The clinical manifestations may be heterogeneous but in some cases one may speak of a syndromic entity, with its own EEG and clinical characteristics and course.
- The role of the cerebral calcification in the genesis and evolution of the epilepsy appears uncertain.
- The role of disease seizure control and in the evolution of endocortical structural lesions cannot be evaluated; the control, whenever obtained, seems to be unrelated to dietary therapy and, moreover, neuroradiological findings were the same regardless of clinical course or compliance with dietary therapy.
- In the absence of positive anato-mopathological results, even the more recent neuroradiological methods do not seem capable of furnishing definitive information with regard to the composition of the deposits shown by CT. In fact, in four of our five cases, MRI and SPECT showed that the cerebral parenchyma was structurally and functionally normal, even in those sites where the CT showed the presence of calcific hyperdensities; only in one case did the
imaging and neurophysiological investigations show a pattern analogous to that of Sturge-Weber disease.

- The neurophysiological examinations (MCV, SCV, SEPs) excluded early involvement of the peripheral nervous system.

Epilepsy

A greater incidence of epilepsy in coeliac disease is described in the literature, even though definitive statistical data do not exist. Recent data lead us to believe that the incidence of epilepsy in coeliac disease is no different from that in the general population. Certain authors have suggested the possibility of a peculiar form of occipital epilepsy in coeliac patients with no cerebral calcification, thus suggesting the need for medical tests (AGA, antiendomysial antibodies) for patients with complex partial seizures, particularly when these are originating in the occipital lobe (Ambrosio et al., 1991; Foss et al., 1994).

In our case studies, epilepsy, although it represents one of the more frequent neurological disorders (8/58, or 13.8 per cent), is almost always associated with a parenchymal atrophic lesions (biocipital or parietal occipital calcifications in five cases, cerebral atrophy in one). Only one patient had complex partial seizures with their focus revealed by EEG in the right temporal lobe. There were no structural lesions on neuroradiological investigation; the seizures were completely controlled by antiepileptic therapy.

Acute cerebral ischaemic

Cortical vascular anomalies, with pial angiomatosia, venous thrombosis and microinfarcts have been recently described in a patient with CEC (Bye et al., 1993), but as early as 1986 the possibility was raised that a possibility of an acute ischaemic episode occurring in an adult with coeliac disease. Neuropathologic findings suggested a vascular phenomenon, probably of an immunologic nature similar to that already been seen in other sites (liver, kidneys) (Rush et al., 1986).

Toxic exogenous substances of bacterial or food origin could be absorbed by the damaged intestinal mucosa leading to the formation of circulating immunocomplexes which could be deposited in the smaller cerebral vessels and provoke vascular phenomena. Furthermore, local inflammatory phenomena could arise following activation of the alternate pathway of complement by the gliadin itself or by the in situ formation of IgA containing immunocomplexes (Gebb et al., 1992; Rush et al., 1998; Ward et al., 1980).

At 30 years of age, our patient was diagnosed as a child but poorly compliant with dietary therapy, had an acute ischaemic episode which began with a headache that worsened over a period of a few days with dysarthria, and transient left bauxitic hemiparesis.

On neurological examination (CT, MRI) the patient showed diffuse cerebral vasculopathy with ischaemic lesions localized in both frontal and parietal areas, more evident on the right side of the right internal capsule (Fig. 5).

The evolution was characterized by periods of well-being alternating with recurrences of transitory ischaemic disorders and headaches, which prompted further investigation. MRI revealed a greater extension of the ischaemic lesions in the right hemisphere, while the focus in the homolateral internal capsule was less evident (Fig. 6).

The bilateral lesions, revealed by the neuroradiological investigations, and their further extension in scans during follow-up examinations, is compatible with the diagnostic hypothesis of vasculitis.

Headaches and migraine

Migrants, among the various neurological disorders manifested during the course of coeliac disease, is quite frequently reported in the literature, whether associated or not with biocipital calcifications.
and epilepsy. The interest in this is related to the fact that the occipital cerebral regions seem to be those more often involved, both in migraine syndromes and coeliac disease. The pathogenic mechanism is unknown, especially in cases without calcifications, although the presence of ‘minor’ vascular/sclerosis phenomena or, in any event, alteration in regional cerebral flow, could be suspected.

Our four cases presented the clinical manifestations of classic migraine (three cases) and common migraine (one case). The cephalic episodes, even though in some cases intense and accompanied by visual symptoms and sensory disturbances, were never very frequent and suspended well to therapy, never leading to a progressive disorder. Convulsive attacks never occurred during the course of the illness. On CT scan, structural anomalies, particularly those of a calcific nature, were absent in all. One migraine episode with flashing scotomas and dysnomia corresponded to slow activity of the theta-delta frequency in posterior location was recorded by EEG.

Cerebral neoplasias

The predisposition to neoplasias in coeliac disease is well known, particularly with regard to lymphomas (50 per cent) and other gastrointestinal neoplasias (25 per cent), although other sites can be involved as well (25 per cent) (Swinson et al., 1981). Deficiency of selenium, as found in coeliac disease and persisting even after dietary therapy, may represent a heightened risk factor in neoplastic pathology. Selenium would carry out its antineoplastic activity by mechanisms in part still unknown, but these would include the ability to protect cell membranes after the mechanism of carcinogenesis and stimulate the immune system (Gregorii et al., 1988).
We know of no cases of cerebral neoplasms associated with coeliac disease reported in the literature. Our cases included a subependymoma of the brain stem and one high frontal cortical astrocytoma. Both patients had been diagnosed as being affected by typical coeliac disease and had been receiving an adequate therapeutic diet early on. The neoplastic lesions occurred, respectively, at the ages of 7 and 12 years. Both patients had partial seizures not fully controllable by drug therapy. In particular, the patient with the frontal astrocytoma began having seizures at 2 years of age; the EEG revealed a slow focus in the right anterior temporal region while a CT scan carried out at 7 years of age gave negative results. The sudden appearance of signs and symptoms of increased intracranial pressure at the age of 12 years led to identification of the neoplastic lesion. The patient later died.

The dosage of selenium administered to the patient affected by the grade I ependymoma of the brain stem was equal to 40 μg (i.e., 107 ± 64 μg whole blood).

Other neurological disorders

Since coeliac disease is not a rare pathology, certain neurological disorders could have only a casual association with it; such is the case with febrile convulsions, which are quite frequent in paediatric age, and with isolated EEG anomalies, especially if localized in the centro-temporal region. Even with regard to psychiatric disorders, so frequently described in the literature and concerning mainly depression and schizophrenia, recent studies have not shown a significant relationship with malabsorption syndrome.

In our study, one patient had learning disability and the other mental retardation with psychotic...
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behaviour. Both children were affected by typical coeliac disease and both were following dietary therapy. Examinations and diagnostic investigations to determine the presence of other risk factors were all negative.

Conclusions

Coeliac disease is associated in a considerable number of cases with neurological pathology. Nonetheless, there are no statistical studies which define with certainty the real incidence of coeliac disease in the individual pathologies. The pathogenetic mechanisms, which are the basis of these pathological associations, have also not been entirely explained. Currently, the neurological disorder most frequently associated with coeliac disease is the cerebral calcifications—epilepsy syndrome, even though certain questions here remain unresolved: why the occipital localisation? What role do the calcifications play in the onset and evolution of the epileptic syndrome? What explanation can be given for the wide-ranging differences in the clinical manifestations of structural lesions which are identical?

Furthermore, nothing is currently known with certainty regarding the mechanism which causes the calcific lesions: the course of the olistico-neuro-radiological aspects presented by our case with acute cerebral ischaemia seems to reinforce the hypothesis that vascular anomalies of an inflammatory nature can play a role in the onset of permanent parenchymal structural lesions.

We also find it worthy of note that in our study there are two instances of cerebral neoplasia associated with coeliac disease. Although the possibility that this association was fortuitous cannot be ruled out, we deem that it warrants further study in order to determine a possible aetiopathogenic correlation, with the aim of improving prognosis and finding possible preventive measures.

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