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Epilepsy, cerebral calcifications and clinical or subclinical coeliac disease. Course and follow up with gluten-free diet

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We have studied four patients (three male, one female, age range 15–25 years) with epilepsy, bilateral occipital calcifications and latent coeliac disease (CD). The epilepsy started at mean age 7 years, in three cases there were partial seizures and in one case generalized seizure. Three cases had symptoms suggesting malabsorptive syndrome during infancy and one case was diagnosed CD before the onset of seizures. In all cases serologic markers of CD were found, especially antiendomisium antibody, and intestinal biopsy indicated several grades of atrophy. The electroencephalograph (EEG) findings pointed to focal abnormalities in three patients and generalized abnormalities in one patient. In all cases computer tomography (CT) showed bilateral, almost symmetrical occipital calcifications in the cortical subcortical layers. The enhanced CT were unremarkable and magnetic resonance images (MRI) were normal. After diagnosis of CD, all patients followed a gluten-free diet and in three patients a significant reduction in seizure frequency was observed. CD should be ruled out in all cases of epilepsy, cerebral calcifications of unexplained origin and malabsorption syndrome in infancy.

Key words: epilepsy; cerebral calcifications; coeliac disease; gluten-free diet.

INTRODUCTION

The association of occipital calcifications, epilepsy and coeliac disease (CD) was first reported by Samaritano *et al*[1] in 1988. Since then, various series of patients have been published in which the presence of cerebral calcifications, epilepsy and CD have suggested the existence of an association or a new syndrome with a possible common genetic origin, without ruling out other aetiopathogenetic possibilities such as those related to folic-acid deficiency.

It is important to know and describe this association or syndrome for diagnostic purposes and in order to begin early therapy, particularly in those patients with poorly controlled seizures who, even without clinical evidence of malabsorption, meet the histopathological and analytical criteria for CD.

We include in our study four new cases of epilepsy, cerebral calcifications and CD and stress the value of gluten-free diet in the clinical course of the neurological symptoms.

PATIENTS AND METHODS

Patients with occipital cerebral calcifications were selected from the Neurology, Neuroradiology and Paediatric Departments and from the clinical records of our hospital.

The inclusion criterion was the finding of occipital cerebral calcifications in computer tomography (CT) with no associated cause after clinical history, physical examination and different diagnosis tests.

The following procedure was followed with the patients included in the study.

1. History: intended to find neurological disease, digestive disease (family and personal history of possible malabsorption syndrome).

2. Physical examination: neurological examination and assessment of possible signs suggesting malnutrition or malabsorption.

3. Additional tests: complete blood count, coagula-

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Table 1: Clinical features of the seizures.

Patient	Sex	Age	Age at onset of seizure	Type of seizure	Frequency of seizures
1	F	18	10	Partial motor	3–4/day
2	M	25	10	Partial visual	2–3/week
3	M	17	2	PCG	2–3/day
4	M	15	10	PCG	1/week

Sex: M, male; F, female. Type of epilepsy: PCG, partial complex generalized.

tion study, complete biochemical testing including (Ca, PTH), protein profile, blood levels of folic acid, vitamin B_{12}, liposoluble vitamins, antigliadin antibodies (IgG, IgA), anti-endomysium antibodies (IgG, IgA) antireticulin antibodies (IgA, IgG).

An intestinal biopsy was obtained in patients with positive antibody titres to confirm the diagnosis of CD.

In patients with confirmed CD diagnosis and clinical signs of epilepsy, additional tests for epilepsy were conducted: electroencephalograph (EEG) (awake and asleep), magnetic resonance imaging (MRI) of the brain and in some cases, SPECT.

In those patients with confirmed diagnosis of CD and epilepsy, a gluten-free diet was instituted with assessment of response to some of the epileptic seizures.

RESULTS

Four patients with occipital cerebral calcifications, CD and epilepsy were selected. All the patients were from Canary Island, without date referring to emigration to other Mediterranean countries, background of Italian ancestors or of blood relationships. The mean age was 18 years with a range of 15–25 years. There was a slight male prevalence of three to 1 female. The neurological examination was normal in all patients. The neuropsychological examination in two of the patients showed a mild cognitive deficit. Table 1 shows the clinical findings.

One patient had a family background of seizures of an unknown aetiology in the mother and one patient had a family background of seizures, including a brother with CD. The disease began with epilepsy in two patients (at the age of 10 years and 8 months respectively) and cerebral calcifications were seen at diagnosis. The others cases were already known to have malabsorption syndrome (at the age of 2 years and 5 months respectively, finally attributed to CD at the age of 5 years and 7 years respectively). These patients developed epilepsy at the age of 26 months without cerebral calcifications in the cranial CT, and 10 years with cerebral calcifications, respectively.

In three patients, the seizures were partial with or without associated visual or occipital symptoms. One patient showed generalized and tonic–clonic seizures. The frequency of seizures was high from the onset (mean 2–3/week).

The EEG showed a slowing down of the basal activity and poor reactivity with frequent focal activity becoming generalized. The abnormal activity consisted of spikes and/or spikes and waves in one or both parieto-occipital regions, often enhanced by eye closure. During the course of the seizure the EEG showed the persistence of paroxysmal abnormalities in all but one case.

In all cases the CT scan showed bilateral, almost symmetrical, occipital calcification in the cortical-subcortical layers. In one case there was parietal calcification. The enhanced CT were unremarkable. The calcifications were cortical-subcortical and linear. Table 2 shows the findings of the CT scan. The MRI study of the calcifications were normal or showed the absence of a signal in the area corresponding to calcification. In two patients SPECT was carried out and one case showed hypoperfusion in the occipital area. All patients showed positive titre of antiendomisium or antigliadin antibodies and the jejunal biopsy showed partial villous atrophy. The values of folic acid were normal in three patients and one patient showed low values.

After diagnosis of CD, all patients were prescribed a gluten-free diet with follow-up every 4 months. Two patients showed a significant reduction in frequency of seizures, one patient was seizure free and the other patient had irregular control. Table 3 shows the follow-up after a gluten-free diet.

DISCUSSION

Epidemiological aspects

Most of the recent reports on epilepsy, occipital calcifications and CD are from Italy[1–11], the rest coming from France[12] and, recently, Spain[13–17] and Argentina[18]. There are few reports in the literature from Anglo-Saxon countries or other nationalities and those are restricted to a few cases[19,20].

Coeliac disease is very common in Italy and the Mediterranean countries[21,22], which is possibly one of the reasons why the syndrome association is more common. In countries with a very low CD prevalence, such as Japan, China and Africa, no patients have been reported to date.

The CD prevalence in Europe ranges from 1/300

Table 2: Cranial CT calcifications findings.

Patient	Localization	Area	Forms
1	Bilateral occipital	Cortical	Linear
2	Bilateral occipital parietal	Cortico-subcortical	Nodular
3	Bilateral occipital	Cortical	Linear
4	Bilateral occipital	Subcortical	Nodular

Table 3: Follow-up after gluten-free diet.

Patient	Follow-up (years)	Seizure frequency	Coeliac control	Changed calcification
1	3	Decreased 30%	Good	No
2	2	Seizure free	Good	No
3	4	Decreased 10%	Irregular	No
4	2	Decreased 50%	Good	No

to 1/2000 inhabitants[23,25]. Eating habits may possibly play some part in the prevalence of CD therefore in those countries with a large consumption of gluten-rich food, both the latent and clinical prevalence of the disease is higher[21,22].

There is no clear prevalence of either sex with regard to frequency, but in the larger series documented to date, there is a slight increase in women, particularly in those previously known to have suffered from CD[10,11]. In our cases, there is a slight male prevalence of 3 male to 1 female.

The average age ranges from 14 to 16 years[10,11]. The mean age in our series was 18 years with a range of 15–25 years. The mean age is probably greater because most of the cases are from an adult neurology department unlike other studies which were conducted in neuropaediatric departments.

EPILEPSY

The epileptic seizures usually begin in early childhood although they have been reported from the first year after birth[10]. In our series, the earliest case began at the age of 2 years.

The epilepsy is usually partial, with or without associated visual or occipital symptoms. Generalized tonic–clonic seizures have also been reported without a clear focal onset. No correlation has been found between the extension of calcifications and the severity of epilepsy. Epilepsy can occur in as many as 5% of patients with CD[26–28] and in these cases it was not associated with cerebral calcification.

The existence of a greater focality is not always in proportion to more widespread calcification. Calcification is possibly not always related to the development of epileptic seizures in these patients and there may be independent foci of occipital calcification. Hence, the evolution time should be suitably assessed, particularly in those cases showing difficult therapeutic control in which new foci of activity may appear.

In most patients with CD and calcifications, epilepsy is hard to control, multiple therapies are applied in many cases and drug-resistance is seen[1,7,10,11,13]. In patients with no previous diagnosis of CD and in whom a gluten-free diet was prescribed, a better control of up to 50% was seen and some of them had no seizures for more than 6 months[10,11,28]. In all our cases, better control of seizures was achieved and in case 2 they remitted for more than 6 months. The changes in the control of seizures do not appear to be related to the age of onset of epilepsy, although they do appear to be related to the duration of epilepsy and diet compliance[10,11].

It has not been established how the institution of a gluten-free diet helps to control the seizures, although there may be pharmacokinetic factors, particularly those related to a better absorption of the antiepileptic drug, owing to normalization of the intestinal epithelium. In our cases, the application of the gluten-free diet has helped to improve the plasma levels of the drug.

Other factors may help to relieve epileptic seizures in these patients, such as correction of anaemia and sideraemia, normalization of folic-acid levels and perhaps other possible metabolic disorders which could influence the control of seizures.

CALCIFICATIONS

The calcifications are located at the occipital level, often bilateral. Other sites, in order of frequency are: temporal, parietal and frontal, sometimes but not always with bioccipital calcifications. In the cases published no changes were seen in the evolutionary course and no changes are usually seen with the administration of contrasts. It is not clear at what moment in the evolution of the disease the calcifications first appear, since in most of the cases published they were seen at the time of diagnosis. In our series, case 3 showed no calcifications at onset of the epileptic seizures and it was only years later, when a

further control CT was made, that the calcifications were seen. The seizures had been badly controlled in this patient and low folic-acid levels were seen during their evolution.

Calcifications are usually cortical-subcortical and linear, and occasionally nodular or serpiginous, similar to those appearing in Sturge–Weber's syndrome, although the calcifications in that syndrome usually change after contrast administration, are associated with microgyria, lobar or hemispheric atrophy and are usually unilateral[29,30]. In Sturge–Weber's syndrome the existence of hypertrophic choroid plexuses and abnormalities in the cerebral venous drainage[31] are usually common. No case of Sturge–Weber's syndrome has been reported with facial naevus and CD.

The MRI study of the calcifications is usually normal or showing the absence of a signal in the area corresponding to calcification[11]. The brain SPECT studies show a decrease in brain flow (hypoperfusion) in calcification sites[9], as occurred in one of our cases.

It is not easy to explain the preference of the calcifications for the occipital level, but it could be due to the selective vulnerability of the occipital lobe[32,33]. It has not been established that a gluten-free diet is able to change cerebral calcifications. The early institution of this diet and a suitable degree of compliance could help to prevent the development of calcification and even of epilepsy itself in these patients.

OTHER NEUROLOGICAL SYMPTOMS

Mild cognitive disorders may often occur in patients with epilepsy calcifications and CD, ranging from retarded psychomotor development to pictures of clear neuropsychological impairment. The inadequate control of epilepsy can enhance neuropsychological impairment[8–10].

Early diagnosis and treatment of CD could help to prevent neuropsychological impairment. Some authors[8,11] have related the good control of the crises and the absence of impairment to a short CD duration.

CD has been reported to be associated with dementia and cerebral atrophy, particularly in adults[34]. The aetiopathogenetic mechanisms in these cases are uncertain, although immunologically based mechanisms have been involved as well as those related to folic-acid metabolism.

COELIAC DISEASE

Since the first descriptions of patients with epilepsy, calcifications and CD it has not been established whether the occurrence of these symptoms and signs signifies an association, or rather, a syndrome. We are inclined to think that it is a syndrome in which the existence of several factors are possibly required to trigger completely the symptomatic triad.

The origin of this syndrome is not clear and can hardly be explained by the existence of CD alone, therefore a common aetiopathogenetic factor should be considered, possibly mediated by some genetic component that might be influenced by a certain situation conditioned by diet or secondary to a metabolic disorder in which folic acid changes could play a significant part. Most of the cases initially described have shown epileptic seizures and cerebral calcifications (mainly occipital), the signs of CD having little clinical significance.

The high prevalence of CD in patients with cerebral calcifications and epilepsy may be similar to that found between dermatitis herpetiformis and CD. All, or almost all, patients with dermatitis herpetiformis have clinical or subclinical CD, whilst only a limited number of patients with CD have dermatitis herpetiformis[35,36].

Familiar cases have been reported of bioccipital calcifications and epilepsy not associated with CD, but with the same immunogenetic HLA markers as the latter[37]. Patients with epilepsy, calcifications and CD often have first-degree relatives with CD but without epilepsy or occipital calcifications as in our cases.

Some patients, as in case 3 of our series, showed no occipital calcification at the onset of the clinical signs of epilepsy, but calcifications occurred associated with frequent seizures. Patient compliance with the gluten-free diet in this case was fairly irregular and low folic-acid levels were seen on several occasions. These factors could possibly have enhanced the development of calcification and the poor control of the epileptic seizures.

The anti-endomysium antibodies are those showing greater specificity and sensitivity, particularly when screening for the disease is being conducted in large populations[22]. On following up patients with CD, it has apparently not been possible to identify any determining factor of the development of cerebral calcification and epilepsy in such patients[18,26].

Different neurological disorders have been reported as related to CD, such as encephalopathy, cerebellar ataxia, dementia, myelopathy and peripheral neuropathy[38–41]. Some of these disorders could be explained by a folic-acid deficiency, although in many of the cases described the folic acid was not measured.

EPILEPSY, CALCIFICATIONS, CD AND FOLIC ACID

Neurological disorders and cerebral calcifications have been found in iatrogenic folic-acid deficiency

(treatment with methotrexate and radiotherapy)[42–46] and in congenital malabsorption of folic acid[47,48].

Calcification in cases of epilepsy, calcifications and CD can be caused by a folic-acid deficiency. In our series cases 3 and 4 showed folic-acid deficiency in some controls of their clinical follow-up, coinciding with a deterioration of the clinical course. No folic acid deficiency was reported in the Sturge–Weber syndrome with facial naevus[49,50].

Certain antiepileptic drugs such as phenytoin could exacerbate the folic-acid deficiency, impairing the clinical condition of epilepsy and possibly enhancing the development of cerebral calcification in these patients[51]. It is also possible that even though the serum and erythrocyte levels are normal, the folic acid could be abnormally absorbed and functionally deficient, as sometimes occurs with impaired vitamin B12 metabolism[52].

There are reports of the association of CD with diseases of autoimmune origin[53–56], in some of which it has been possible to recognize a folic-acid deficiency, which could enhance the onset of the clinical triad.

The folic-acid deficiency, combined with the genetic disorder of CD, may be the cause of the primary calcification process of the vessel wall and the cerebral parenchyma at the level of the occipital cortex and the parallel or sequential development of epileptic seizures.

In the treatment of the disease, folic acid must be administered in cases of deficiency and in those cases that are in the lower normal limits, and also the possibility of parental (intramuscular) administration should be considered until the CD parameters are normal.

In countries where the consumption of gliadin-rich foods is common, the possibility of the presence of CD should be considered in patients with epilepsy (particularly when resistant to therapy and of unknown origin) or with cerebral calcifications.

Further studies are needed to establish the aetiopathogenetic bases of this complex and interesting syndromic association.

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