Severe epilepsy preceding by four months the onset of scleroderma en coup de sabre

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ABSTRACT

Juvenile localized scleroderma (JLS) includes several subtypes including plaque morphea, linear scleroderma and the en coup de sabre type which affects face and head. The latter variety may involve the eye and the brain with various appearance and clinical complications.

We describe the case of a 6-year-old boy who presented partial complex seizures, with status epilepticus, four months before the appearance of sclerodermatous skin lesions on the face. This case report raises important questions on the pathogenesis of JLS and, particularly, on the issue whether it is a mere autoimmune condition or a neuro-cutaneous disease.

Introduction

Juvenile localized scleroderma (JLS) refers to a number of different conditions characterized by circumscribed and asymmetrical areas of skin thickening and induration, including plaque morphea, linear scleroderma, generalized and pansclerotic morphea (1, 2)

Linear scleroderma (LS), one of the most frequent subtypes of localized scleroderma in children usually affects upper or lower extremities but can also develop on the face or scalp, as in the *en coup de sabre* (ECDS) or Parry Romberg syndrome (PRS) varieties (3). ECDS consists in linear-shaped induration that affects the face or the scalp often compared to a stroke from a sword (sabre), usually on the paramedian forehead. PRS, named also progressive hemifacial athrophy (PHA), results in hemiatrophy of the face where the primary lesion occurs in the subcutaneous tissue, muscle and bone. The relationship of PHA to ECDS is unclear but studies on long term follow up of patients with these two conditions (4) and others showing similar prevalence of CNS and ocular involvement and autoantibody profile (5-10) seem to confirm that they are different manifestations of the same pathogenic process, involving mainly the superficial skin in ECDS and mainly subcutaneous tissue, muscle and bone in PRS.

Central nervous system (CNS) involvement, consisting of chronic headache, epilepsy, hemiparesis or mental retardation, has been reported by several authors in both ECDS and PRS (4, 11) and usually develops concurrently or after the appearance of skin lesions.

Herein we describe the case of a child with ECDS in which both neurological symptoms and typical MRI lesions appeared months before the onset of the cutaneous involvement.

Case report

A 6-year-old caucasian boy, with an unremarkable previous medical history, suddenly developed partial complex seizures with unilateral left clonic jerks treated with e.v. bolus of diazepam. One month later he was admitted to the intensive care unit of the Bologna Children's Hospital for refractory non-convulsive status epilepticus characterized by absence-like persistent loss of consciousness and followed by a prolonged generalized tonic-clonic seizures. He was promptly treated with a phenitoin bolus, midazolam and propofol, and intubated and mechanically ventilated.

Cerebral MRI revealed small cortical and subcortical areas of hyperintense signal on T2 weighted and FLAIR sequences in the paramedian and basal regions of left frontal lobe which showed slight enhancing following intravenous gadolinium (Fig. 1)

Discharged from hospital one week later, the neurological evaluation was clinically normal, as well as visual and brain stem auditory evoked potentials,

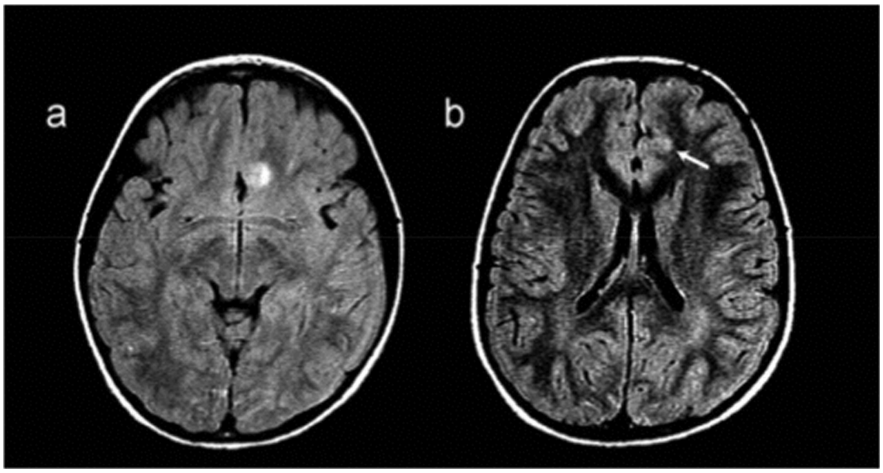

Fig. 1. MRI at disease onset. Small areas of high-signal intensity in the left frontal lobe basal (**a**) and paramedian (**b**) regions (white arrow) (axial FLAIR).

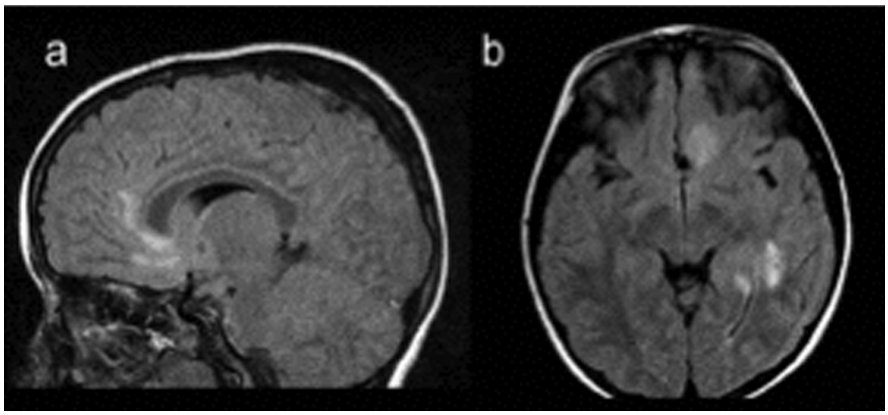

Fig. 2. MRI investigation follow-up after 3 months. (**a**) Significant increase of the left frontal lobe lesions (sagittal FLAIR). (**b**) New lesions in posterior temporal lobe, involving the periventricular white matter (axial FLAIR).

ophthalmologic assessment and cerebrospinal fluid analysis. Verbal and performance intelligence quotient (IQ) were estimated to be respectively 79 and 91 according to the Wechsler Intelligence Scale for Children (WISC).

Epilepsy was treated with clobazam and oxcarbazepine with fairly good control of seizures. However, since the onset of epilepsy, learning disabilities, hyperactivity and oppositional behaviour have been noticed.

Laboratory examinations, including complete blood cell count, liver and renal function tests, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), polymerase chain reaction and serology for neurotropic viruses, antiphospholipid and antinuclear antibodies (ANA), were negative or within the normal range.

Control cerebral MRI, respectively 1 and 3 months later, showed new lesions, with intense enhancing after gadolinium infusion, in posterior medial temporal lobe with involvement of the periventricular white matter (Fig. 2). Moreover, the previously observed frontal lesions appeared significantly increased with small T2*-weighted gradient-echo hypointense spots, consistent with calcified areas.

Four months after the onset of seizures, the boy presented a small oedematous and erythematosus area on his left cheek, initially misdiagnosed as allergic contact dermatitis and treated with antihistaminic drugs with no benefit.

Subsequently, the lesion became slowly indurate and hyperpigmented, extending down to the left nasal ala and up to the ipsilateral malar and suborbital regions, to involve, with two bands the forehead. During the following months, the parents noticed asymmetry of the face due to a progressive left facial atrophy, the scalp was spared and the diagnosis of scleroderma ECDS/PRS was then made (Fig. 3).

Treatment with oral prednisone (1mg/kg/day) and methotrexate (15mg/m^2/week sc) lead to an improvement of both skin changes and behavioural abnormalities. Prednisone was stopped after 3 months and methotrexate after a year.

At the three-year follow-up, an MRI showed regression of the white matter abnormalities which were replaced by juxtacortical and subependymal calcifications, as shown by CT scan (Fig. 4).

Discussion

In a large series of 750 patients with JLS, CNS involvement has been reported in 4.4% of the patients. This frequency raises up to 18% in patients with linear scleroderma of the face (ECDS/PRS) (3).

Epilepsy is the most frequent reported symptom followed by headache, hemiparesis, mental retardation, behavioural changes, and learning disabilities (3, 11, 12). These symptoms are not always associated with detectable brain lesions but sometimes can be preceded by the occurrence of them, without a clear correlation between severity of brain abnormalities and clinical picture (13).

When neuroradiological abnormalities are detected, they are predominantly ipsilateral to the skin lesion and can be found also in neurologically asymptomatic subjects (12, 13). Focal subcortical calcifications, involving basal ganglia, thalami and dentate nuclei, and hyperintense lesions of the white matter on the T2-weighted MRI are the most common reported neuroradiological findings (14-18). However, vascular malformations, migrational defects, CNS vasculitis, meningeal enhancement and cerebral atrophy, have also been reported (14, 18, 19). This has led to the formulation of several hypothesis about the mechanisms underlying the brain involvement in this condition.

According to some authors, since the facial tissues and underlying brain parenchyma have a common cell progenitor, an early malformation, affecting one side of the rostral neural tube can

cause, later in life, cerebral and facial ipsilateral lesions (20).

Another possible explanation might be to consider ECDS-PRS among the neurocutaneous syndromes or the result of abnormal angiogenesis (21), cortical dysgenesis (20), or sympathetic overexcitation (22-24). However, to date, the immunological hypothesis considering a neurovasculitis at the basis of the neurological disease seems to be the most commonly accepted and shared explanation (25-27). According to this hypothesis, a focal cerebral inflammation, especially of the vessels, can cause reactive gliosis and then intraparenchymal calcifications (21).

An inflammatory rather than a dysgenetic process may be also supported by the recent observation that, in one third of patients, neurological abnormalities are unrelated to the site of skin involvement (11).

In most of the patients, the development of neurological manifestations follows the recognition of the cutaneous disease with a time interval of months, or even years. To date, very few cases with neurological symptoms preceding the characteristic skin involvement have been reported (17, 28, 29). In only one, however, cerebral MRI, performed in a girl with new-onset partial epilepsy, detected a mild hippocampal atrophy before the skin lesion recognition (29). However, since the lesion was on the scalp and localized scleroderma sometimes expands very slowly, it might be possible that it was already present at the time of the onset of seizures. Moreover, hippocampal atrophy is an unspecific neurological abnormality, unusual in scleroderma ECDS (30) and therefore not unequivocally related to it.

Our patient is the first one in whom both typical white matter hyperintense lesions on the T2-weighted MRI and seizures were unequivocally present several months before the onset of the cutaneous disease.

The neuroradiological findings, at follow-up, documented a dynamic process underlying the neurological symptoms. An acute phase, characterized by inflammatory changes (hyperintense lesions on T2-weighted MRI with enhancing after gadolinium infusion as sign of blood-brain barrier damage) was followed by a subacute phase, with slow resolution of the lesions on MRI, and by a final stage characterized by calcification of the lesions observed both on CT scan and MRI. These abnormalities are strongly consistent with an inflammatory process preceding the cutaneous disease and partially confirming the neurovasculitis hypothesis. Therefore, although the link between cerebral and facial involvement remains

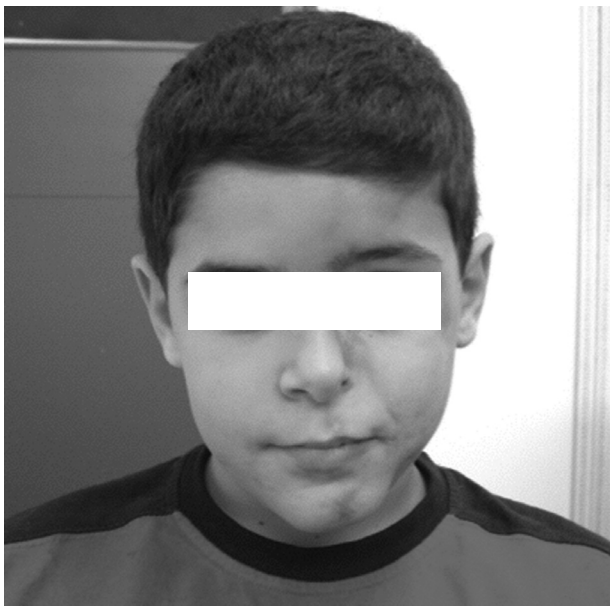

Fig. 3. Appearance of the face three months after the first skin changes, and seven months after the seizures. Areas of induration and hyperpigmentation following a linear disposition and associated with initial facial hemiatrophy

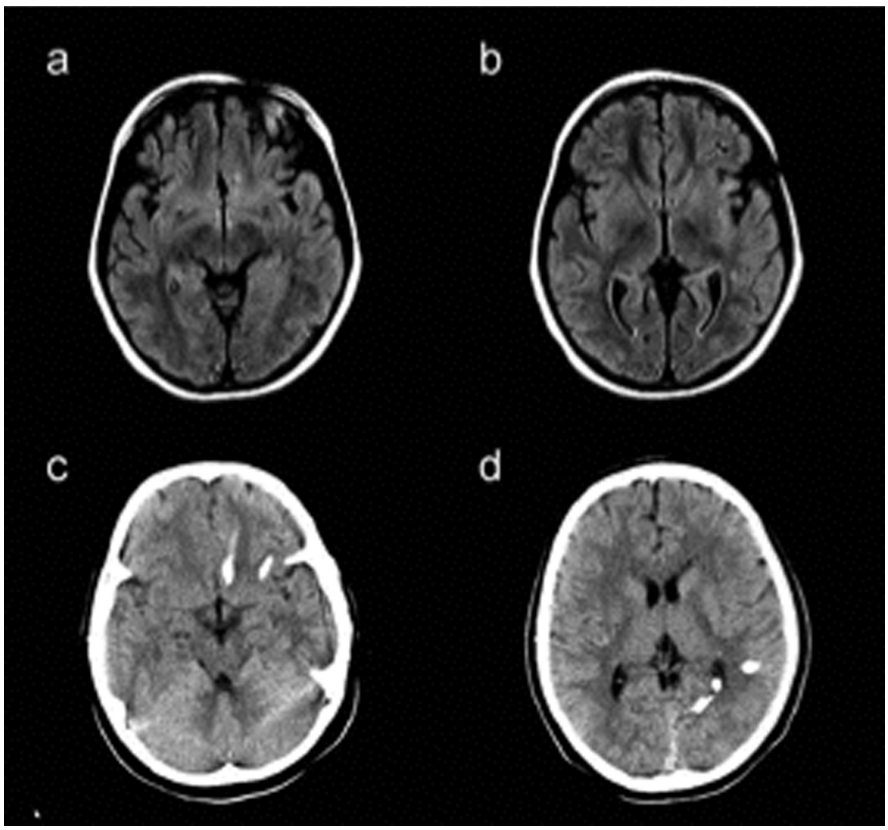

Fig. 4. Neuroimaging follow-up after 3 years. MRI showing regression of previous white matter abnormalities in the left frontal (**a**) and temporal lobes (**b**) (axial FLAIR). CT scan showing juxtacortical and subependymal calcifications, at the left frontal (**c**) and temporal (**d**) lobes, at the same sites where the MRI lesions had been previously visualized.

unclear, these data seem to support the possibility that a neurological inflammatory process – not always clinically evident – may represent the "primum movens" of the skin involvement. (31). In this perspective, the unilateral character of the disorder might be explained by a one-sided vulnerability of skin and brain tissue, due to an early malformative event of the rostral neural tube. This process has been suggested, for example, for Rasmussen syndrome (32), a chronic localized encephalitis, affecting a single brain hemisphere with progressive unilateral atrophy, clinically characterized by controlateral hemiplegia, intractable focal motor epilepsy, and progressive intellectual deterioration.

Our case underlines the importance of considering scleroderma ECDS in the differential diagnosis of patients with new-onset partial seizures, as well as other unexplained neurological manifestations, particularly in the presence of potentially evocative neuroradiological findings.

In these patients, a careful examination of the skin, with particular attention to the face and scalp, should be performed and repeated over time.

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