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CASE REPORT

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Systemic lupus erythematosus and myoclonic epileptic manifestations

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Abstract Systemic lupus erythematosus (SLE) frequently involves the central nervous system (CNS) and, in fact, epileptic manifestations may be one of the earliest symptoms of SLE. These early occurrences of epilepsy, however, can easily be misdiagnosed as indication of pure epileptic syndrome when the SLE diagnosis is still largely incomplete.

We present a young girl who developed myoclonic photosensitive seizures at the onset of the illness, erroneously diagnosed as manifestation of a "pure" epileptic syndrome. Shortly after the onset of an anticonvulsant therapy (lamotrigine), there was a remarkable impairment of the general clinical condition: at that time a diagnosis of SLE was made and a specific treatment began. However, the seizures persisted and evolved toward status epilepticus which needed pentobarbitone therapy in an intensive care unit (ICU). After recovery, the girl gradually got better and during the 23 months of follow-up she received only corticosteroid therapy and did not experience seizures nor SLE relapses.

Key words SLE • Myoclonic epilepsy • Status epilepticus • Lamotrigine

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Introduction

System lupus erythematosus (SLE) involves the central nervous system (CNS) in 20%-74% of patients [1-3]. The clinical features cover a wide range of symptoms from mild depression and cognitive behavioral abnormalities to headache, severe psychiatric disorders, movement disorders, stroke and epilepsy. Reports are not consistent relative to the incidence of epilepsy. The seizures are usually described as generalized (tonic-clonic type) or partial (simple or complex); they are reported either as one of the first symptoms of the SLE illness or as a late complication from it [4, 5]. These studies seldom include comments on the electroencephalogram (EEG) pattern or the recurrence of the epileptic manifestations.

In this paper we describe the case of a young girl whose myoclonic photosensitive seizures at the onset of the SLE illness were erroneously diagnosed as "pure" epileptic syndrome.

Case report

R.M., female, was born in April 1983 after a 40-week normal pregnancy. The birth weight was 3450 grams. Her family had no history of neuropsychiatric illness and her neuropsychological development could be considered normal. Some behavioral disturbances (prevailingly of the obsessive type), however, were present since infancy. The menarche occurred when the patient was 10.7 years old.

In 1993, at the age of 10, R.M. began experiencing headache and insomnia, and her behavioral disorders became more remarkable. In October 1996, R.M. experienced persistent high body temperature (37.5°C-38°C) and the following month she gradually developed discontinuous dyskinetic movements of the axial muscles and/or the proximal extremities of the superior limbs, asthenia, lack of

appetite (she lost 6 kg body weight), pharyngitis and fever. For these symptoms R.M. was hospitalized in an infectious illness unit where hematological tests evidenced positivity for antinuclear antibodies (ANA), antinative DNA, Dixon test, and Epstein-Barr visus-viral capside antigen (EBV-VCA) IgM. Hepatosplenomegaly, lymphoadenopathy and moderate thrombocytopenia (93 000/mm^3) were also found. On the basis of these data, a diagnosis of mononucleosis was made and, because of the persistence of the dyskinetic movements, an EEG was performed.

EEG recording at rest showed generalized short-lasting discharges of polyspike and wave (PPO) complexes, with or without clear-cut clinical correlates. More prolonged PPO discharges, observed during hyperventilation (HV) and intermittent photic stimulation (IPS), were always accompanied, however, by myoclonic jerks of the trunk and limbs.

Within a few days the patient's symptoms substantially regressed and she was discharged from the hospital with a diagnosis of mononucleosis and epilepsy.

Our first observation was in January 1997; at that time the girl was attending school with moderate success. She had persistent but mild headache and behavioral disorders, and showed mild signs of ataxia and sporadic uncoordinated movements of the trunk and limbs. We also observed myoclonic jerks of the head, trunk and superior limbs, which her parents explained as tics.

Brain magnetic resonance imaging (MRI), performed some days before our check, had revealed a few small areas of hyperintense signal in the subcortical white matter, interpreted as non-specific cerebral lesions by the radiologist.

A standard EEG showed background alpha activity mixed with slow waves of theta frequency (Fig. 1a). HV and IPS recorded generalized short-lasting epileptic discharges. The discharges were characterized by one group of polyspike and wave complexes followed by some slow waves, diffuse, with higher amplitude on the anterior regions, and were accompanied by myoclonic jerks of the trunk and the limbs (Fig. 1b, c). An ambulatory 24-hour EEG showed 145 generalized discharges with a mean duration of 1.53 s, 108 occurring during wakefulness and 37 during nocturnal sleep, mainly at sleep onset and upon awakening (Fig. 1d).

We prescribed an anticonvulsant therapy with lamotrigine, with an initial dose of 0.3 mg/kg day for one week and successive increases of up to 0.6 mg/kg day. Within five days of this therapy the myoclonic epileptic jerks decreased but the following symptoms appeared: a fever resistant to antipyretic treatment, a rash on the face and trunk, and diffuse arthralgias. Four days later the patient was again hospitalized in the Unit for Infectious Illness because of a progressive impairment of the general clinical status and the appearance of an intermittent mental slowing to a confusional state.

The hematological tests revealed: ANA ++++; antinative DNA ++++; anti-extractable nuclear antigens (ENA) +; anticardiolipin = 52 (normal value, 0-20); Dixon test +; erythrocyte sedimentation rate (ESR) = 60; platelets = 820 x 10^9/l; lactate dehydrogenase = 5888; creatine kinase = 1133; AST

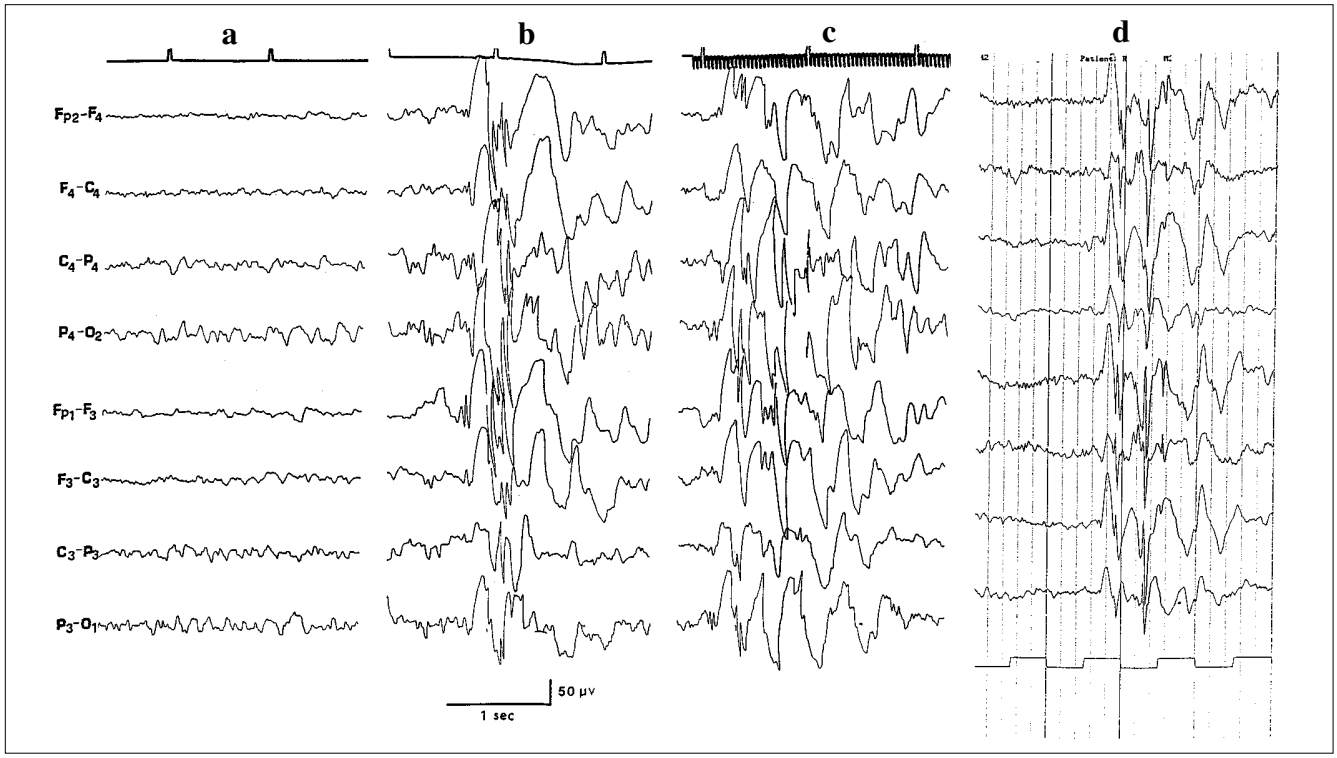

Fig. 1a-d *Four samples of EEG tracings recorded at the onset of the illness.* **a-c** Standard EEG. Theta activity in the posterior regions is observed at rest (a), while generalized discharges of polyspike and wave complexes are recorded during HV (b) and IPS (c). **d** An example of the 145 generalized epileptic discharges recorded during ambulatory 24-hour EEG

= 2284; ALT = 721; AP = 286; PT = 45%; antithrombin III = 120%; myoglobin = 212; gammaglobulinemia = 38%. A diagnosis of SLE with CNS involvement was finally made based on the clinical symptoms and the lab tests. Lamotrigine therapy was immediately interrupted and a treatment with methylprednisolone, cyclophosphamide and plasmapheresis was initiated.

A progressive impairment of the clinical condition followed with appearance of signs of disseminated intravasal coagulation (DIC), rhabdomyolysis and myopericarditis. Moreover, recurrent generalized myoclonic and tonic-clonic seizures, refractory to benzodiazepine administration, began to occur, rapidly evolving toward status epilepticus. The patient was transferred to the intensive care unit (ICU) where she was intubated and a status of coma was induced with pentobarbitone to obtain seizure control. The specific therapy for SLE was never interrupted. Three days later, there was a progressive improvement of the clinical condition and pentobarbitone administration was gradually reduced with recovery of consciousness. At the same time an antiepileptic treatment with clonazepam (6 mg/kg day) was prescribed. Weekly EEG did not show any epileptic abnormality, while MRI showed multiple small periventricular and subcortical focal lesions, indicative of cerebral vasculitis.

In March 1997, the girl was finally discharged from the hospital in good clinical condition. She gradually returned to her normal occupations, experiencing only mild signs of ataxia, slight movement disorders and behavioral alterations for about three months. Anticonvulsant therapy (clonazepam, 6 mg/day) was interrupted just 1 month after release from the hospital.

In the 23 months since her discharge from the hospital, she has continued her prednisone treatment, with daily dosage now of 12.5 and 25 mg, alternatively, and she has suffered no relapses of SLE. ANA are still positive (+++) but antinative DNA antibodies are negative and anti-cardiolipin antibodies are in normal range.

After recovery from status epilepticus, no further epileptic seizures occurred. EEGs, performed every three months, progressively evolved toward normalization, without epileptic abnormalities both at rest and during the activation procedures (IPS and HV). MRI performed 12 months after hospital discharge documented a remarkable reduction of the vasculitis signs, with the presence of multiple small areas of gliosis.

Presently, the patient is able to attend to her normal daily activities; however, because of a remarkable impairment of the psychopathological features, during the last months she has submitted to a therapy with fluvoxamine with good results.

Discussion

Epileptic seizures are relatively frequent in patients affected by SLE with cerebral involvement. When the epileptic manifestations represent one of the first signs of the illness, they may be erroneously interpreted as “pure” epileptic manifestations without proper identification of the specific pathology.

In the case of our patient, an initial diagnosis of mononucleosis was made, even if some biological data were already suggestive for SLE. Furthermore, the EEG pattern and the clinical characteristics of the epileptic attacks, very suggestive of a form of a primary generalized myoclonic epilepsy, had a share in misleading physicians who did not correlate the underlying illness and the epileptic manifestations. On the other hand, generalized tonic-clonic seizures, rather than myoclonic seizures, are usually reported in SLE.

It is interesting to note that both the epileptic discharges and the myoclonic seizures could be evoked by IPS: these characteristics allow linking our case to that reported by Brinciotti et al. [6]. These authors described the case of a girl whose initial manifestations of SLE consisted in reflex partial seizures (visual and acoustic hallucinations), induced by visual and acoustic stimulations. The seizures appeared ten months before the clinical symptoms of SLE, and they were diagnosed and treated as a form of partial epilepsy.

About the pathophysiological mechanisms of the epileptic manifestations, it is possible to hypothesize a role of the small, high-density cerebral lesions observed at MRI: these lesions, reversible or fixed, thromboembolic in nature, seem to be highly correlated with the presence of anti-phospholipid antibodies [7]. Quantification of these antibodies was not performed in our patient: however, it is interesting to observe that the epileptic manifestations were particularly active during the strongest phase of the illness, when the lesions were more pronounced.

Prolonged periods of treatment with some classic antiepileptic drugs (AEDs) such as carbamazepine, valproate, phenytoin, ethosuximide and primidone may occasionally cause the appearance of SLE. No relapses occur after the interruption of AEDs [8]. In the case of our patient, the explosion of the acute manifestations of SLE (with its cerebral involvement) appeared some days after the onset of the anticonvulsant therapy with lamotrigine. A direct involvement of lamotrigine in the SLE induction may be excluded in this case because: (a) the initial symptoms of the illness presumedly preceded lamotrigine administration, and (b) 23 months after the diagnosis of SLE and interruption of the drug, laboratory tests showed persistence of the illness. The role of lamotrigine in the precipitation of the acute and severe clinical episode cannot be excluded, however, even though administered at low dosage for a short period of time.

The specific therapy for SLE resulted in the complete disappearance of the clinical and electrographic manifestations of epilepsy. The patient is free of seizures after 23 months, and the EEGs do not show any epileptic abnormality either at rest or during activation procedures, even when no anticonvulsant drug is administered. Similar results were reported by Brinciotti et al. [6]. It is therefore possible to hypothesize that the remission of the epileptic manifestations is due to the good control of SLE, epilepsy being only an

acute symptom of the illness. Alternatively, the disappearance of the clinical and electrographic epileptic manifestations could be correlated to the corticosteroid treatment, to which the patient is still submitted.

Clearly, the relation of myoclonic epilepsy and SLE are not yet fully understood and this is certainly a fertile area for future research work.

Sommario *Il coinvolgimento del sistema nervoso centrale (SNC) nel lupus eritematoso sistemico (LES) è molto frequente e le manifestazioni epilettiche possono rappresentare uno dei primi sintomi della malattia: la loro precoce comparsa, quando ancora non sono chiari i segni specifici del disturbo di base, può renderne più difficile la corretta diagnosi.*

Presentiamo il caso di una giovane ragazza che, quale primo sintomo più evidente del LES, ha presentato un pattern elettroclinico suggestivo di epilessia generalizzata di tipo mioclonico, con fotosensibilità. Pochi giorni dopo l'inizio del trattamento anticonvulsivante (lamotrigina a basse dosi), si è osservato un grave peggioramento delle condizioni cliniche generali: i tests di laboratorio hanno permesso la diagnosi di LES ed è stato intrapreso il suo trattamento specifico. Tuttavia, le crisi persistevano e si è sviluppato uno stato di male convulsivo per il controllo del quale si è resa necessaria la somministrazione di pentobarbitone. Interrotto lo stato di male, la paziente è gradualmente migliorata e nei successivi 23 mesi non si sono osservate né recidive della malattia di base, né la ricomparsa di altre manifestazioni critiche, anche in assenza di trattamento antiepilettico.

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