Syndrome Resembling Systemic Lupus erythematosus Induced by Carbamazepine

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Key Words

SLE-like syndrome
Carbamazepine
Antinuclear antibodies
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Anticonvulsant and hypnotic drugs produce side-effects in 15-25% of treated patients. The frequency of cutaneous and systemic reactions increases with higher drug serum concentrations. Carbamazepine (Tegretol) is chemically related to imipramine (Tofranil); both can induce pruritus, maculopapular exanthema, vasculitis, erythema and facial oedema, exfoliative erythroderma as well as toxic epidermal necrolysis [1]. 'Collagen disease' due to carbamazepine was described by Simpson [2] in 1966. In the literature, there are 3 cases of systemic lupus erythematosus (SLE) induced by carbamazepine, 3 cases of SLE aggravated by carbamazepine and 1 case of discoid lupus erythematosus due to carbamazepine. Antinuclear antibodies (ANA) in patients on anticonvulsant therapy have first been described by Alarcon-Segovia et al. [3, 4]. A 40-year-old secretary was operated on because of a right sylvian aneurysm in January 1994. Her left arm remained paralysed; because of a right epileptic focus she was given carbamazepine 400 mg daily. One year later, she was seen for red macules of the face and Raynaud's phenomenon of the extremities, the left paralysed arm being more affected. After Raynaud's attacks, the arm remained cyanotic for a prolonged period of time. Pink and violaceous cutaneous papules were seen over the phalangeal and carpal joints and were present in a more dispersed manner on the arm and the dorsal face of the hand which exhibited a lichenoid appearance. Laboratory investigations showed a normal white blood cell count, normal electrolytes and urea and normal liver enzymes. ANA were positive at a titer of 1/320 (table 1). Because of scheduled holidays on the Canary Islands, she was prescribed chloroquine sulphate 100 mg/day. In February 1996, she was seen with complaints of pain and burning of the face and arms. The skin was reddened with a photosensitivity-like distribution. The histology of two biopsies performed 6 months later on the dorsum of the hand and the forearm showed a packed infiltrate of lymphocytes and histiocytes in the dermis invading the basal layer associated with typical 'colloid bodies'. A diagnosis of lichen-planus-like eruption was made. Laboratory investigations showed γ -glutamyltransferase at 32 IU/l (normal 4-18), carbamazepine at 10.4 μ g/ml (normal 4-10). The

ANA titer had increased to 1/1280. HLA typing of the patient was HLA A3, A24, B7, BX, DR15 (DR2), DR4. Carbamazepine was replaced by sodium valproate (Depakine) 3×500 mg daily. Six months later, the ANA titre was unchanged, but anti-DNA antibodies and antihistone antibodies became negative. The cutaneous lichenoid lesions improved progressively.

The clinical aspect first had the appearance of lichenoid lesions which were confirmed histologically. Further appearance of photo-sensitivity and Raynaud's phenomena pointed to a more systemic condition. The suspicion of drug-induced lupus was strengthened by the auto-antibody profile of the patient (table 1). The absence of anti-native-DNA antibodies immunofluorescence and the absence of antichromatin (antinucleosome) antibodies by the immunodot method are arguments against an idiopathic form of SLE. The presence of antihistone antibodies which disappeared when the carbamazepine treatment was discontinued are also arguments for a drug-induced lupus-like syndrome. Idiopathic SLE is found to be preferentially associated with the HLA antigen DR3 [5] and less to DR2. On the contrary, drug-induced lupus has been found to be associated frequently with HLA DR4 [7], especially in lupus induced by hydralazine in slow acetylators patients. The patient described here exhibited HLA DR4 and DR2. Based on the clinical improvement after carbamazepine withdrawal, the auto-antibody profile and its evolution, we assume that this patient had a carbamazepine-induced lupus-like syndrome.

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Table 1. Evolution of ANA pattern in our patient

Antibodies	Tegretol			
	12.1.1995	14.2.1996		
Depakine	8.10.1996	26.11.1996	24.12.1996	12.2.1997
Nuclear pattern	1	dots++	dots++	
Cytoplasmic pattern	1	-	++	
Titre	1/320	1/1280		
Anti-dsDNA (ELISA)	< 50	negative	> 200	
Anti-nDNA (Crithidia lucilae)		negative	negative	
Antihistone	negative	86		
Anti-Sm/RNP	-	+		
dots	+++	dots +++	dots +++	dots +++
	++	+	-	-
	1/1280	1/1280	1/1280	1/1280
	> 200	> 200	negative	negative
	negative	negative	negative	negative
	47	negative	negative	negative
	+	+	+	+

Immunofluorescence on HEP-2 cells.

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Lamotrigine and Toxic Epidermal Necrolysis

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Key Words

Lamotrigine · Toxic epidermal necrolysis · Valproic acid

Cutaneous rash is one of the commonest adverse events associated with lamotrigine, especially among patients already taking valproic acid. The risk of developing severe skin reactions including toxic epidermal necrolysis (TEN) is low [1]. We describe a patient with myoclonic epilepsy receiving valproate who developed TEN 14 days after initiating lamotrigine therapy. A male child aged 22 months was admitted to the Department of Pediatric Infectious Diseases on December 27, 1996 with a 3-day history of fever and rash. He was the first child in a 3-member family, born after an uncomplicated 40-week gestation. He had a history of viral meningoencephalitis at the age of 4 months. Treatment-resistant myoclonic epilepsy developed after the meningoencephalitis. Since valproate treatment resulted only in a poor control of epilepsy, lamotrigine was added on December 11, 1996, at an initial dose of 1 mg/kg/day increased after 10 days to 2 mg/kg/day. During this period of combined therapy, the patient became seizure free, but fever and a maculopapular rash developed on the 14th day of therapy and

the patient was admitted to the pediatric intensive-care unit (PICU). On admission the child appeared very sick, severely dehydrated, prostrated with high fever (39.8 °C) and with a sunburn-like rash covering two thirds of the skin surface which rapidly evolved to blisters. Lamotrigine was then discontinued, but the eruption worsened and TEN involved the conjunctivae, oral cavity and trachea. A skin biopsy was done which confirmed the diagnosis of TEN. Histologically, necrotic keratinocytes within the epidermis, vacuolar alteration of the basal layer and subepidermal blisters were present. The clinical course of illness was protracted and complicated by a nosocomial *Enterobacter cloacae* infection. After 4 weeks in the PICU, the patient recovered totally.

A cutaneous rash develops in about 5% of patients starting lamotrigine [1]. The risk of developing TEN is very low [1], although a fatal outcome of TEN occurring under treatment with lamotrigine was reported in a patient previously treated with carbamazepine [2]. The incidence of a rash is increased in patients receiving concomitant valproate therapy [1]. Valproate inhibits lamotrigine metabolism and alters the half-life of lamotrigine by as much as

100% [3]. Therefore, the gradual increase in the lamotrigine dose in patients already receiving valproate therapy is advised. Most of the patients reported developed skin reactions within 2 weeks after starting lamotrigine that is compatible with the development of immune sensitization [4]. In previous studies lamotrigine was well tolerated and effective for various types of seizure [5]. We suggest that lamotrigine should be considered as a cause of unexplained cutaneous rashes, particularly in patients where lamotrigine therapy is combined with sodium valproate.

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