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Development of Chorea with Lupus Anticoagulant after Interferon Therapy

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Choreiform syndromes have many etiologies, including systemic lupus erythematosus (SLE), certain drugs, and the presence of lupus anticoagulant (LA) [1]. In addition, many drugs are capable of inducing lupus-like states. We report a case of chorea with LA in a girl treated with human recombinant interferon alfa-2a (IFN) for chronic myelogenous leukemia (CML).

A 10-year-old girl came for consultation in November 1992 complaining of clumsiness of the left upper limb. Her previous history included CML diagnosed in 1987. Coagulation parameters, including activated partial thromboplastin time (APTT) and diluted thromboplastin time (DTT), were normal. Antinuclear antibodies (ANA) and LA were not sought. Treatment with daily oral hydroxyurea (HU) and subcutaneous injection of IFN (5,000,000 units) was begun in December 1987. HU was stopped in January 1988, IFN was continued, and cytosine-arabinoside (10 mg/m² subcutaneous injection for 10 days each month) started. The course was favourable, with complete cytogenetic remission. In May 1989, IFN was continued at the same dose 5 days/week, then 5,000,000 units for 4 days and 3,000,000 the 5th day, followed by 2 days without therapy. In October 1990, the blood was positive for ANA with homogeneous fluorescence and antibodies against native desoxyribonucleic acid (DNA). The APTT was slightly prolonged, but the DTT, using diluted tissue thromboplastin 1/40, was normal. In March 1992, the APTT was further prolonged, and the DTT was positive. An antipro-thrombinase type of LA was found (table 1). In October 1992, IFN was reduced to 3,000,000 units 5 days/week. In September 1992, her teacher, and the child herself noted progressive difficulty in writting accompanied by abnormal movements, principally of the upper limbs and head. Her handwriting, which had been neat, became irregular and at times hardly legible. A diagnosis of chorea was made. The coagulation tests showed prolonged APTT (table 1) in association with LA. The other coagulation parameters were normal. Quantitative determination of cardiolipin antibodies (immunoenzymatic assay) and complement were normal and serological tests for syphilis were negative. ANA and antibodies against DNA were positive (table 1), but antibodies against soluble antigens and antihistone antibodies were negative. The direct Coombs test was positive. Anti-streptococcal antibodies did not reach a significant level. Thyroid hormone concentration was normal. Cerebrospinal fluid study, electroencephalogram and magnetic resonance imaging of the brain were normal. Bone marrow aspiration confirmed the complete cytogenetic remission of CML, and IFN therapy was thus discontinued. In December 1992, she was given venoglobulins at a dose of 0.4 g/kg/ day for 5 days, followed by very low-dose haloperidol (1 mg/day) for a month together with corticosteroids (prednisolone 1 mg/kg/day) for 2 months. In January 1993, the abnormal movements had greatly diminished in intensity, amplitude and frequency. Handwriting normalized within 2 months. From February 1993, she underwent no further treatment. In July 1993, neurological and hematological examination were normal, but the coagulation tests continued to show the presence of LA. A platelet neutralization procedure confirmed the antiphospholipid nature of the anticoagulant. ANA were positive, while native anti-DNA antibodies were negative (table 1). In December 1994, neurological examination was normal, and the patient remained in cytogenetic remission. ANA were slightly positive but antibodies against native DNA were absent. No LA could be detected; the APTT was normal and the DTT was negative (table 1). In this case, discovery of a lupus syndrome with circulating LA preceded the appearance of chorea by 2 years. A link between the lupus syndrome with LA, IFN and chorea is highly probable, since other etiologies of chorea cannot be retained. The advent of chorea during remission of the leukemia, the normal results of complementary examinations and the remission of symptoms in the absence of treatment argue against a tumoral origin or a paraneoplastic syndrome. Among the central nervous system manifestations of SLE, chorea is rare (3%). It can exist in the absence of LA; it frequently reveals the disease, and is often associated with neuropsychiatric symptoms [1]. However, in our young patient, the diagnosis of SLE cannot be retained. Similarly, chorea can be associated with LA without any other clinical or hematological sign of SLE, and may exceptionally reveal acute lymphoblastic leukemia [2]. The association of antiprothrombinase antibodies and ANA without any clinical evidence of SLE can be encountered in hematological disorders such as CML and in the course of treatment with various drugs [3]; but our young patient was not treated with such drugs. The change over time of ANA, anti-native-DNA antibodies, and the LA levels was parallel to the institution and subsequent discontinuation of IFN treatment, and not with the progress of CML. The appearance of many autoim-

Table 1. Coagulation data

APTT	
DTT	
ANA	Anti-DNA
	patient, s
ratio	control, s
	patient, s control, s mixture,
s	
antibodies	

	(patient/control)
f control)	(patient
October 1990	
41	
29	
1.4	
35	37.5
	36.5
	1/500
1/100	
March 1992	
67	
32	
2.1	
47	
30	
43	
ND	
ND	
October 1992	
58	
29	
2.0	
105	
50	94.5
	1/1000
1/500	
July 1993	
83	
29	
2.9	
124.5	
50	
101	1/100
	negative
December 1994	
34	
30	
1.1	
48	
54	
48	
1/50	
	negative
ND = Not done.	

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immune disorders has already been observed in patients receiving long-term treatment with a-IFN [4]. Several authors have reported the appearance of SLE, but without chorea or LA, after a median of 20 months of treatment with IFN for CML [5, 6] and for a carcinoid tumour [7]. The clinical and laboratory manifestations of SLE regressed following the discontinuation of IFN treatment. Conversely, and in the absence of any treatment, raised levels of endogenous a-IFN have been observed in SLE and other autoimmune conditions. Some authors believe that endogenous a-IFN may constitute a marker for disease activity, since its level correlates with levels of ANA and anti-native-DNA antibodies, as well as with the clinical activity of SLE, particularly the psychiatric manifestations [8]. It can thus be argued that a-IFN carries a risk of SLE, as has been found in an animal model [9]. The pathogenesis of chorea associated with LA is multifactorial. It may be due to lacunar infarction of basal ganglia by vasculitis. However, in many cases, no lesion has been detected by MRI or at autopsy. Conversely, there may be diffuse lesions which were detected radiologically or at autopsy, which would not directly explain the chorea. It is possible that antiphospholipid antibodies are directly responsible by causing an autoimmune encephalopathy. These antibodies could damage the blood-brain barrier, allowing the passage of autoantibodies which react with the brain [10]. This observation of chorea with circulating LA, probably induced by IFN and reversible after its discontinuation, confirms that chorea can be associated with different physiopathological mechanisms, and must be added to the other neurological manifestations of IFN treatment which have been previously described.

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