Cerebral lupus erythematosus responding to plasmapheresis

D. T. P. EVANS*
M.B., M.R.C.P.(U.K.)

M. GILES†
M.B., Ph.D.

D. J. de L. HORNE‡
M.Phil., Ph.D.

A. J. F. d'APICE†
M.B., M.D., F.R.A.C.P.

A. RIGLAR¶
M.Sc.

B. H. TOH§
M.B., Ph.D., F.R.A.C.P.

**Clinical Research Unit, The Walter and Eliza Hall Institute of Medical Research, †Departments of Psychiatry and Nephrology, The Royal Melbourne Hospital, ‡Department of Psychiatry, University of Melbourne, §Department of Pathology and Immunology, Monash University Medical School, and ¶Department of Medicine, Austin Hospital*

Summary

A 44-year-old nurse with a 12-year history of systemic lupus erythematosus developed a schizophrenia-like psychosis due to cerebral lupus. Prednisolone in doses up to 200 mg daily was ineffective. Levels of immune complexes by the Raji cell assay were greatly increased in serum and cerebrospinal fluid. Plasma exchange was performed on 4 occasions over 4 days. Three days later, there was a marked and sustained improvement in the mental state, the psychosis resolved and tests of psychological function and electroencephalographic abnormalities improved. There was a corresponding decrease in levels of immune complexes and in titres of anti-neuronal antibody. Five months later, several serological indices had risen to pre-plasmapheresis levels except for the level of immune complexes. The patient remained in clinical remission. This case provides further evidence that high levels of circulating immune complexes may be a determinant of cerebral lupus and that plasmapheresis may be of lasting benefit in this disease.

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease attributable in a large part to deposition or formation in the tissues of immune complexes. Plasma exchange has been used in immune complex-mediated glomerulonephritis (Becker *et al.*, 1977; Dunadio, 1977) to reduce levels of circulating immune complexes, and mediators of tissue injury such as complement components and

procoagulants. Rossen *et al.* (1977) described a patient with SLE, with renal and cerebral involvement, in whom treatment with cyclophosphamide, prednisolone and repeated plasma exchange led to neurological remission and reduction in circulating immune complexes. However, in another case of cerebral lupus with a normal serum level of immune complexes, a plasma exchange up to 18.6 litres produced no improvement (Verrier-Jones *et al.*, 1978). In a patient with SLE and a schizophreniform psychosis, reduction by plasmapheresis of high levels of circulating immune complexes and anti-neuronal antibody induced rapid and sustained improvement.

Case report

The patient developed SLE in 1967 at the age of 32, and had been treated intermittently with prednisolone. Disease activity continued with episodes of episcleritis, giant urticaria, diarrhoea, colic and erythematous rashes. In December 1978, when prednisolone had been withdrawn for 3 months, her husband noted a change in mood and personality and thereafter there were periods of irrational uncharacteristic thought and behaviour. In March 1979, prednisolone 10 mg per day was recommenced; however, the mental symptoms persisted, and she was treated with trifluoperazine, chlorpromazine, and benztropine to control her psychosis.

She was admitted to the Clinical Research Unit in March 1979. The only abnormal physical findings were moderate alopecia and an erythematous macular rash on the face and upper trunk. She was dishevelled, restless and showed inconstant disorientation in time and place. There was pressure of

Correspondence: Dr I. R. Mackay, The Walter and Eliza Hall Institute of Medical Research, Post Office, Royal Melbourne Hospital, Victoria, 3050, Australia.

speech with grandiose and delusional content. Mood was elevated. She showed thought disorder characterized by derailment, loosening of association and interpenetration of personal themes. She also complained of gustatory hallucinations. There was gross impairment of attention and concentration and to a lesser extent short-term memory, but remote memory was relatively intact. An electroencephalogram was abnormal, whilst a CAT brain scan was normal.

There was no improvement with large doses of neuroleptic drugs including thioridazine, chlorpromazine, and haloperidol. Prednisolone in doses up to 200 mg daily was equally ineffective. The lack of response to the combination of anti-psychotic drugs and high doses of prednisolone prompted treatment by plasmapheresis, on days 35–38 after admission.

Investigations showed Hb 11.6 g/dl; ESR 80 mm/hr (Westergren); WBC $11.8 \times 10^9/l$ and lymphocytes $0.95 \times 10^9/l$; serum iron, 6.6 $\mu\text{mol/l}$. The HLA phenotype was A1, A3 : B7, B8. Serum IgG was normal, but was increased in the cerebrospinal fluid (CSF) (0.06 g/l; normal <0.03 g/l). The LE cell test was positive, the titre of anti-nuclear antibody by immunofluorescence was 1 : 1000, the level of anti-DNA binding activity (see Methods) was 340 u./ml (normal <25 u./ml), and the levels of serum complement components were serum C3, 53 mg/dl and serum C4, 30 mg/dl. Immune complexes were extremely high in serum, >3000 and 1610 $\mu\text{g/ml}$ of aggregated gamma globulin equivalent per ml on 2 occasions (normal 0–40 μg) and also in CSF, 80 $\mu\text{g/ml}$ (mean for controls, 8.85 $\mu\text{g/ml}$).

Methods

Immune complexes

Immune complexes were assayed in serum and cerebrospinal fluid by 3 methods. The Raji cell radioimmunoassay was performed by the method of Theofilopoulos, Wilson and Dixon (1976), except that 0.25 μg ^{125}I -labelled protein A in 50 μl of medium was used in the final incubation instead of ^{125}I -rabbit anti-human IgG.

Because sera from patients with SLE react in the Raji cell radioimmunoassay after ultracentrifugation, presumably owing to antibody reactive with the Raji cell surface, all sera for this assay were tested before and after ultracentrifugation with the difference representing the true level of immune complexes (A. G. Riglar and I. F. C. McKenzie, in preparation).

The Clq binding assay for immune complexes was performed by the method of Nydegger *et al.* (1974) and Zubler and Lambert (1977), and the polyclonal rheumatoid factor assay by the method of Cowdery, Treadwell and Fritz (1975).

DNA binding activity was measured with the

Standard Anti-DNA Kit (Amersham, Bucks, England). Anti-neuronal autoantibody was tested for by indirect immunofluorescence with viable monolayer cultures of mouse neuroblastoma cells (neuro-2a, Flow Laboratories) as described by Tohti and Mackay (1981). For immunofluorescent tests, the cells were subcultured on glass coverslips in 35-mm culture dishes and incubated for 24–72 hr at 37°C and rinsed in buffer.

Bound immunoglobulin was detected with FITC-labelled goat anti-human immunoglobulin. All tests were carried out in parallel with PBS and normal human serum controls. The immunoglobulin class of the sera was determined by the tests with FITC-labelled goat anti-human IgG, IgA or IgM.

Plasmapheresis

This was performed using an Amminco continuous flow centrifuge (Americal Instrument Company, Silver Spring, Maryland). The replacement solution was Stable Protein Plasma Solution (SPPS).

Results

Clinical observations

Four 4-litre plasma exchanges were given, further exchanges being precluded by the occurrence of a left lower lobar *Klebsiella pneumoniae*. Three days after the fourth plasma exchange, there was a marked improvement in the mental state with resolution of the psychosis, insight into the nature of the illness and loss of disorientation. After 4 weeks, improvement was maintained, the dose of prednisolone had been reduced to 15 mg daily and all psychotropic drugs had been withdrawn. An electro-encephalogram which had shown irregular activity of 7–8 cycles per second with moderate excess of theta activity became normal after plasma exchange.

Laboratory studies

After plasmapheresis, there was an immediate fall to zero in the serum level of immune complexes by the Raji cell assay, with no increase for 60 days (Table 1). The maximum level after plasmapheresis was 250 $\mu\text{g/ml}$, recorded after 138 days. Assays for immune complexes by binding to Clq and to polyclonal rheumatoid factor showed only slight and unsustained reductions after plasma exchange.

Serum DNA binding antibody levels 2 days after plasmapheresis had fallen from 128–340 u./ml and the maximum level after plasmapheresis was 37 u./ml.

The titre of anti-neuronal antibody fell from 80–160 to undetectable levels on the second day of plasma exchange, but thereafter increased gradually until pre-plasmapheresis levels were reached even though there were no overt neurological abnormalities.

TABLE 1. Serial changes in serum immune complexes (3 assays), DNA binding antibody and anti-neuronal antibody titres with time. Plasmapheresis performed on 26/4/79 – 29/4/79 inclusive

Date of serum sample	Days after admission	Assays for immune complexes		PRFA	DNA binding antibody (u./ml)	Anti-neuronal antibody titres
		Raji assay (µg/ml)	ClqBA (µg/ml)			
2/4/79	11	> 3000	0.5	0.6	340	160
5/4/79	14	1610	0.5	0.7	380	80
17/4/79	26	1200			230	80
23/4/79	32				128	
26/4/79	35	1600	0.5	0.9		
27/4/79	36	395	0.1	0.4		< 5
28/4/79	37	14	0.1	0.4		10
29/4/79	38	0	0.1	0.3		< 5
Post-plasmapheresis						
1/5/79	40				13	
9/5/79	48	160			32	
15/5/79	54	0	0.2	0.4	30	5
21/5/79	60	32	0.2	0.5	28	160
30/5/79	69	0			38	160
28/6/79	98	0	0.2	0.4		160
14/9/79	176	250	0.7	0.7		160
17/10/79	209	115	0.9	0.6		
28/5/80	433	46				
Normal		< 40	< 1.0	< 1.7	< 25	

TABLE 2. Psychological test results

	Before plasmapheresis (3 days before)	After plasmapheresis (12 days after)	Follow-up (23 days after)
Mill Hill vocabulary test IQ	105	103	114
Standard progressive matrices IQ	< 75	–	84
Benton visual retention test			
(i) Correct	2	–	4
(ii) Expected correct	8	–	8
Wechsler memory scale IQ	73	92	90
WMS subtest raw scores			
Current information	2	4	4
Orientation	1	4	5
Mental control	7	7	8
Logical memory	1	8	7
Digit span	9	10	9
Design memory	6	4	7
Verbal associate learning	13	15	10

Psychological tests

Psychological test results (Table 2) indicated that before treatment, orientation for time and place was markedly impaired. Short-term memory was severely impaired although short-term concentration was normal. Verbal Associate Learning was performed well.

Two days after the last plasmapheresis she became rational and co-operative and fully orientated in time and space. She showed some insight into her illness and spontaneously recognized her previous

poor compliance with medication. This improvement was maintained and 8 days after plasmapheresis she demonstrated a good understanding of current affairs, considerable improvement in memory, could perform serial sevens accurately, continued to have no delusions, and showed good short-term memory and registration to informal testing. She was able to interpret proverbs well, and correctly remembered the Babcock sentence. Formal psychological testing was done before plasmapheresis and 12 and 23 days after the last treatment. The changes

FIG. 1. Graph of immune complexes (Raji assay), DNA binding antibody and anti-neuronal antibody titres before and after plasmapheresis. Also charted are prednisolone and haloperidol dosage.

observed indicated localized cortical dysfunction and documented the significant improvement which followed plasmapheresis (Table 2). At follow-up 9 weeks later, improvement in mental state was maintained and she had returned to her previous active life. At the time of her follow-up in October 1980 she was still well.

Discussion

The patient described fulfilled the criteria for diagnosis of SLE proposed by the American Rheumatism Association (ARA) in 1971 (Editorial, 1975) in that 6 of the 14 specified criteria were present.

She had an organic psychosis and the diagnosis of cerebral lupus was made on the basis of neuropsychiatric features occurring in a patient with established SLE (having excluded effects of corticosteroids or other agents), EEG changes, a raised level of IgG, and increased anti-DNA binding activity in the cerebrospinal fluid. The level of CSF cyclic GMP, which has been correlated with neuropsychiatric manifestations of SLE (Kassan and Kagen, 1978) was not measured in the present case.

The pathogenesis of cerebral lupus is uncertain. There is evidence for the presence in CSF of anti-neuronal antibodies which are either specific for neuronal antigens or are cross-reactive with lymphocyte antigens (Bresnihan *et al.*, 1979). However, the data of Winfield, Brunner and Koffler (1978) do not

support direct involvement of either DNA/anti-DNA complexes, or of lymphocytotoxic antibodies cross-reactive with brain cells.

Post-mortem studies have shown deposits of immunoglobulins and complement within the choroid plexus, and it has been suggested that deposits of immune complexes within the choroid plexus may affect permeability sufficiently to allow circulating anti-neuronal antibody access to cerebral tissues (Atkins *et al.*, 1972). Immunofluorescent tests for anti-neuronal antibodies on the patient's sera showed a dramatic drop in antibody titres after plasmapheresis with a return to pre-plasmapheresis levels after 3 weeks. The observations that the patient has remained asymptomatic and that the levels of the Raji assay immune complexes have remained depressed suggest that both elevated immune complex levels and anti-neuronal antibodies are necessary for the development of cerebral lupus. The data are consistent with the suggestion that the blood brain barrier needs to be breached by immune complex-mediated cerebral vasculitis before anti-neuronal antibodies can penetrate the brain. Anti-neuronal antibodies, cytotoxic for neuroblastoma cell lines, demonstrated by immunofluorescence, have also been reported by others (Wilson *et al.*, 1979; Bluestein, 1978).

There is evidence for the presence of Fc receptors in normal human choroidal tissue (Braathen and Førre, 1980). These receptors may bind K-cells producing damage *via* the classical complement

pathway; alternatively, they may bind immune complexes which block the choroid plexus. Exacerbation of cerebral lupus being associated with raised levels of immune complexes in the CSF has not been previously reported.

Plasmapheresis in SLE is being increasingly used (Leading Article, 1979) and the indications for plasmapheresis in cerebral lupus are becoming clearer. A favourable response can be anticipated if there are high levels in serum of immune complexes and antibodies to double-stranded DNA before treatment (Rossen *et al.*, 1977; Verrier-Jones *et al.*, 1978) and, as judged from the present case, high levels in CSF of immune complexes may be a predictor of benefit.

Documenting the changes in mental state in cerebral lupus, and improvements or otherwise as a response to a particular treatment is difficult owing to the need to quantify what is usually a subjective assessment, and psychological testing was undertaken to provide a basis for objective assessment in the present patient. That the improvement in mental state was due to plasmapheresis rather than the anti-psychotic medication seems very likely in view of the temporal relationship between plasmapheresis and the improvement in mental state, the lack of response before plasmapheresis and the fact that response to anti-psychotic medication is usually more gradual than in the present case. It might be informative to perform isotope $^{15}\text{O}_2$ or xenon brain scans before and after plasmapheresis.

The beneficial mechanisms attributable to plasmapheresis remain speculative. In the short term there is presumably a reduction of the agent(s), anti-neuronal antibodies or immune complexes, which determine the pathogenesis of cerebral lupus. The long-term benefit, exemplified by the present case, may be attributable to abrogation of the process of autoimmune amplification described by Hall *et al.* (1977). Finally this case suggests that shorter than conventional courses of plasma exchange may be effective in ameliorating the course of SLE.

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