Human immunoglobulin subclasses of antimitochondrial antibodies and total serum immunoglobulin* and IgG subclass† values in patients with primary biliary cirrhosis

Case No	Sex	Age	IgG Subclass				Antiserum 8a4 (anti-IgG Fc)	IgG	IgA	IgM	IgG1	IgG2	IgG3	IgG4
			IgG1	IgG2	IgG3	IgG4								
1	F	51	+	—	W	—	++	12.00	1.20	2.95	125	110	190	<10
2	F	59	—	—	+	—	++	15.05	2.85	2.60	210	225	600	70
3	F	60	+	W	++	—	++	19.95	1.95	9.10	350	225	1400	95
4	F	52	—	+	++	+	++	15.80	3.00	5.35	100	120	1050	75
5	F	30	—	+	+++	—	+++	19.05	3.45	2.20	190	225	1050	25
6	F	51	—	—	++	—	++	18.30	4.10	9.00	45	145	1600	10
7	M	62	—	—	++	—	++	ND						
8	F	80	—	W	W	—	+	16.25	4.60	2.35	260	75	775	160
9	F	59	—	—	++	—	++	ND						
10	F	53	—	W	W	—	W	35.85	3.80	3.13	600	250	900	200
11	F	63	—	—	+	—	+	11.85	2.10	1.40	80	200	160	200
12	M	68	—	W	+	—	++	12.90	1.25	2.70	125	160	800	10
13	M	65	—	+++	+	+	+++	15.00	1.95	3.05	160	380	1250	10
14	F	76	—	—	+++	—	+++	23.05	2.05	2.80	350	120	1650	125
15	F	52	W	—	++	W	++	ND						
16	F	60	+	+	++	+	++	23.20	2.00	10.40	260	240	1350	90
17	F	60	W	+	++	+	+++	18.45	3.30	7.65	175	150	950	125
Normal range (mean)								6.00–16.00	0.75–4.00	M: 25–200 F: 50–240	72–128	58–154	60–150	35–200

W = "Weak" positive.
ND = Not done.

*Serum immunoglobulin concentrations expressed as g/l.
†Serum IgG subclass values expressed as % of standard pool.

human serum. Fluorescence was scored as either negative (—), weak positive (W), or definite positive (+ to +++).

Serum immunoglobulin concentrations were measured by automated laser nephelometry. IgG subclasses were measured by the single radial diffusion test. Sera from 17 patients (14 women) with the clinical and biochemical features of primary biliary cirrhosis were referred from physicians in the West Midlands. All had a positive, classic mitochondrial antibody on routine laboratory testing, with clinical and laboratory findings consistent with the diagnosis.

The table gives the results in the sera from the 17 patients. Antimitochondrial antibodies occurred in all four subclasses. IgG3 was the most consistent and appeared in all 17 patients, IgG2 in 10 patients, while IgG1 and IgG4 antibodies were each found in only five patients.

The IgG3 antibodies also appeared to be the predominant subclass, in that in all except one of the sera they gave the most intense fluorescence; in the exception (case 13) the antibody was predominantly in the IgG2 subclass. In a further extensive study of the subclass distribution of antinuclear antibodies in patients with systemic lupus erythematosus and rheumatoid arthritis (Riggioni and Thompson, unpublished observations) this subclass restriction was not observed. The serum IgM and IgG concentrations were significantly increased in the patients ($p < 0.001$) as compared with the controls. Within the IgG subclasses IgG3 was greatly increased ($p < 0.001$). IgG1 and IgG2 were also significantly increased ($p < 0.01$) but to a less degree. There was no significant difference in IgG4 values.

Comment

In analysing IgG antibody responses several IgG subclass restrictions have been described both in animal models and in man^{3,4} and changes in the distribution of IgG subclasses have also been reported in disease.

Antimitochondrial antibody, which is a hallmark of primary biliary cirrhosis, was found predominantly in the IgG3 subclass, though in many patients weaker activity in other subclasses was also present. Since IgG3, which fixes complement readily, represents only about 8% of normal IgG this is a significant restriction in subclass expression. A restriction to this subclass has not previously been described for autoantibodies. While the role and significance of antimitochondrial antibodies in primary biliary cirrhosis is unknown, their strong association with this condition at least suggests that the aetiological factors which initiate the disease are similar to those that result in the formation of these particular antibodies.

Restriction of antibody responses to IgG3 has been reported in certain viral infections.⁵ Viruses have been implicated as aetiological factors in many autoimmune conditions, and our finding possibly provides some insight into the aetiology of the disease.

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³ van der Gienssen M, Groenboer-Kempers O. The subclasses of human IgG antibodies against tetanus toxoid. *Clin Exp Immunol* 1976;25:117-21.
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Effect of 1050 mg fluphenazine decanoate given intramuscularly over six days

The standard dosage of intramuscular fluphenazine decanoate for schizophrenia is usually below 100 mg a week and seldom exceeds a few hundred mg a week even in exceptional cases. We report a case of accidental overdosage, with more than 1g being given over several days.

Case report

A 24 year old Chinese woman had been diagnosed as a case of childhood psychosis, schizophreniform type, at the age of 9 and had been receiving institutional care at this hospital since the age of 18. During the first four years of her stay she had been given various maintenance regimens of phenothiazine but without effect and remained childish and self absorbed, was ambivalent about going home, and showed little interest in ward activities and occupational therapy. From the age of 22 fluphenazine decanoate 50 mg every four weeks had been added and there was a small improvement.

In February 1982 she suffered two grand mal fits and was transferred to Queen Elizabeth Hospital for investigation. During her stay there her treatment was continued except that in error the fluphenazine was given every four hours instead of every four weeks. The error was discovered on the sixth day, after 21 injections (1050 mg). She appeared to have no ill effects and resuscitative measures were not required. She had no more convulsions and was transferred back to this hospital three days later.

On her return she was in the same childish but cheerful state. At the beginning of the third week after overdosage, however, hypothermia and tachycardia were noted, and one week later features of parkinsonism appeared. Axillary temperatures ranged from 35.6° to 36.7° and the heart rate from 90 to 120 beats/min. She had immobile facies and was salivating and showed a rigid gait. These effects lasted one month, during which she was

observed without specific treatment. Once the effects wore off she was given oral chlorpromazine 50 mg three times a day.
Interestingly, after this episode her behaviour was improved. Electroencephalography and a brain scan showed no focus of epilepsy.

Comment

Adverse effects of high dose depot neuroleptic injections have been reported,¹ but the *Index Medicus* contains no report after dosage as high as in the present case.
This case shows that fluphenazine decanoate is fairly safe in over-dosage. The perplexing factor was the delay in occurrence of toxic effects till three to four weeks later, which then lasted for one month. Pharmacokinetic studies² show that each injection of fluphenazine is followed by a rapid rise in plasma concentration of the drug to a maximum at one to eight hours, which over the next 12-36 hours falls to a value slightly above that before the injection and remains stable until the next injection. Hence the maximum toxic effects would be expected to occur within the first few days after overdose. A possible explanation for the delay may be the effect of very high blood concentrations of the drug on neurotransmitters other than dopamine—for example, an anticholinergic effect would balance out the parkinsonian effects; and not until the drug concentration fell to a more usual value would the toxic effects start to appear.
The improved behaviour of this patient after overdosage may suggest a possible therapeutic effect of megadosage fluphenazine in cases refractory to more usual dosages. This has been reported before: McClelland *et al* found that a regimen of 250 mg a week appeared more effective than 12.5 mg a week and did not produce greater side effects.³ Further research is needed.

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Continuous electroencephalographic recording to detect seizures in paralysed newborn babies

A muscle relaxant is often given to abolish spontaneous respiratory activity in babies who require artificial ventilation. Paralysis abolishes the clinical signs of neurological complications, particularly seizure activity, which may follow hypoxic brain damage, hypercapnia, or

other biochemical abnormality. Some studies have suggested that repeated seizures lead to permanent neurological sequelae.^{1,2} We report seizure activity, detected by a new method of continuous electroencephalographic monitoring, in three babies paralysed while receiving intensive care. This technique permitted prompt diagnosis and rapid assessment of anticonvulsant treatment.

Patients, methods, and results

The table gives the clinical details of the three babies studied. In each case a continuous record of the electroencephalogram, electrocardiogram, and respiration (transthoracic impedance) was made on to a small four channel, battery powered tape recorder (Medilog 4-24 recorder; Oxford Medical Systems, Abingdon, Oxfordshire). Recording was started as soon as possible after paralysis was induced and continued until the neuromuscular blockade was stopped. Standard electrodes were used to obtain bipolar frontoparietal records of the electroencephalogram on the right and left. To reduce artefact from movement the electrodes and miniaturised pre-amplifiers (HDX-82; Oxford Medical Systems) were attached to the scalp by collodion. The skin electrode impedance was less than 5 kΩ and the frequency response 0.5-100 Hz. The electrocardiogram and transthoracic impedance were recorded from electrodes on the chest wall.
Data obtained over 24 hours were recorded on to a standard C120 cassette tape and analysed by replay through a visual display unit (PMD12 Virgo special; Oxford Medical Systems) at 60 times the recorded speed. Each tape was reviewed at intervals that were determined by the findings—that is, after anticonvulsant treatment or after a change in the clinical condition of the baby.
Seizure activity was recorded in the three babies (table). Continuous recording of the data did not interfere with intensive care, and no more than 10% of any tape was obscured by artefact. There were no complications, regular ultrasound scanning of the brain through the anterior fontanelle was possible, and the major part of the scalp remained available for intravenous cannulas.

Comment

Sick newborn babies are at risk of neurological disorder after perinatal asphyxia, intracerebral haemorrhage, metabolic disturbance, or meningitis. The incidence of clinical seizures is as high as 3%,³ but muscle relaxation prevents seizures being diagnosed. Studies in animals have shown that repeated seizures in the neonatal period adversely affect brain growth and result in permanent neurological sequelae, even when hypoxaemia is avoided.^{1,2} Seizures may be the presenting sign of a neurological disorder that requires investigation and treatment, and early diagnosis and control of the seizures may improve the prognosis. The American National Collaborative Perinatal Project found that cerebral palsy and mental retardation were related to the duration of the longest seizure.⁴ In addition, children were 55-70 times more likely to have cerebral palsy or mental retardation if they had had neonatal seizures.⁴
Diagnosis of seizures in paralysed babies depends on electroencephalography, but intermittent recordings are unreliable. Continuous recording with conventional apparatus is impractical, but this new method detects all seizure activity throughout the period of paralysis. Seizure activity was recorded in all three babies but would not have been diagnosed without continuous monitoring. The monitoring also permitted an assessment of the efficacy of anti-convulsant treatment.
Motor end plate blockade in very sick newborn babies prevents a clinical assessment of the neurological state of babies who are at high risk of brain damage. Continuous electroencephalographic monitoring may disclose abnormalities and lead to appropriate investigation and early effective control of seizure activity.

Clinical details and results of electroencephalographic monitoring

Case No	Sex	Gestation (weeks)	Birth weight (g)	Clinical details	Duration of electroencephalographic monitoring (h)	Clinical signs of seizure before paralysis	Electroencephalographic findings	Results of other investigations
1	M	40	3800	Severe birth asphyxia, aspiration of meconium, pulmonary hypertension	48	None	Left sided paroxysmal rhythmic 8-9 Hz "α like" activity; right sided suppression	
2	M	41	2930	Severe birth asphyxia, aspiration of meconium, pulmonary hypertension	72	None	Left sided paroxysmal burst of rhythmic 10-11 Hz "α like" activity	Computed tomography: infarcted left hemisphere
3	M	26	1200	Severe hyaline membrane disease, recurrent pneumothorax, intraventricular haemorrhage	72	Multifocal clonic jerks	Right and left synchronous paroxysmal bursts of rhythmic sharp waves 1-3 Hz of long duration	Ultrasonography: intraventricular haemorrhage