Infantile spasms and HLA antigens

Infantile spasms (IS) or West's syndrome is an epilepsy of early infancy (Gibbs *et al.*, 1954) with a typical clinical picture (salaam spasms, Blitz-Nick-Salaam-Krämpfe), and often a characteristic EEG with hypsarrhythmia. About 90% of the infants will end up with severe psychomotor retardation (Jeavons *et al.*, 1973). Most cases fall into one of two groups, cryptogenic or symptomatic. The cryptogenic group presents after uncomplicated pregnancy and birth, with normal psychomotor development until the appearance of the spasms, and with no abnormal laboratory findings. The symptomatic group shows abnormalities *before* the onset of spasms (infections or trauma during pregnancy, perinatal asphyxia, cerebral or meningeal infections, epilepsy, psychomotor retardation) and/or more specific abnormalities—such as faulty cerebral architecture (Huttenlocher, 1974), inborn errors of metabolism (Bignami *et al.*, 1966), or chromosome-linked diseases such as tuberous sclerosis and Down's syndrome.

These abnormalities seem to have little in common, so the theory was put forward, that IS does not form a nosological entity, but is the clinical manifestation of a stereotyped reaction of the (immature?) brain to widely different influences (Watanabe *et al.*, 1973). A particular genetic disposition might predispose to such a reaction. If so the HLA antigens of patients with IS could perhaps be genetic markers of such a disposition.

In January 1976 a prospective study of children presenting with IS was begun, centred on the paediatric departments of Rigshospitalet, Copenhagen. All children with IS were reported by each paediatric department in Denmark. The results for the first year of the study, with special reference to the HLA antigens, are presented here.

Patients and methods

During 1976 21 newly diagnosed children with IS were reported. At the end of 1976 personal contact was made with all the departments to ensure that no child with IS had escaped attention. The child's sex and date of birth, the age at onset of the spasms, EEG at first admission, the presumed aetiology, blood group, and HLA type were recorded. EEGs were obtained before treatment with ACTH or corticosteroids. HLA typing for the A, B, and C series antigens was performed by the microlymphocytotoxic test (Kissmeyer-Nielsen and Kjerbye, 1967). The distribution of the HLA antigens in both cryptogenic and symptomatic cases was compared with that in 1967 normal adults.

Results

Table 1 gives the clinical and laboratory data of the 21 children, 11 boys and 10 girls. The average age at onset of IS was 6·2 months. In 90% of the cases the EEG showed hypsarrythmia or modified hypsarrhythmia. In 10 cases (5 boys and 5 girls) the aetiology was unknown, whereas in 11 cases there had been either severe neonatal asphyxia or meningitis. The frequency of the blood groups was—A 64%, B 9%, and O 27%; 91% were Rh+ and 9% Rh—.

The HLA types are given in Table 1, while the frequency of the HLA antigens, compared with those of 1967 blood donors, is shown in Table 2. The HLA antigens did not differ significantly from those in the controls, either for the cryptogenic or symptomatic cases, or for the two groups combined.

Discussion

The number in our series, 21, agrees with the reported incidence of IS of about 1 per 3000–4000 live births. The mean age at onset, frequency of hypsarrhythmic EEG, and presumed aetiology were also consistent with reports (Jeavons and Bower, 1964). The sex distribution of 1:1 in our cases is not significantly different from a boy:girl ratio of 2:1, which most authors report (Jeavons and Bower, 1964). Neither in the patient group as a whole nor in the cryptogenic or symptomatic group did any of the HLA antigens differ significantly from that of the 1967 controls. Smeraldi *et al.* (1975) found a significantly higher incidence of HLA-B7 in children with Lennox-Gastaut syndrome, but there was no increased incidence of this antigen in our patients.

The Lennox-Gastaut syndrome is a disease of seizures of early childhood, and has certain resemblances to IS, with the typical seizure pattern of myoclonic-astatic petit mal, a peculiar EEG, and the likelihood of severe psychomotor retardation (Beaumanoir *et al.*, 1968). Up to 25% of children with Lennox-Gastaut syndrome have previously suffered from IS (Chevrie and Aicardi, 1972). Further investigation of the genetic markers of children with IS thus seems justified, both as to a possible connection with the Lennox-Gastaut syndrome, and to a possible marker of IS or disposition to IS. The finding of such a genetic marker might enable us to identify infants at risk, and eventually to devise means to prevent this grave disease from developing.

Table 1 *Details of 21 children with infantile spasms arising during 1976*

Case	*Sex*	*Date of birth*	*Onset of IS (months)*	*EEG at first admission*	*Aetiology*	*Blood type*	*HLA type*
1	M	16/06/75	7	Hypsarrhythmia	Purulent meningitis	O Rh+	Aw19, 24, B12
2	M	07/04/75	9	Modified hyps.	Neonatal asphyxia	—	A1, Aw24, B12, Cw3
3	F	09/08/75	5	Hypsarrhythmia	Cryptogenic	—	—
4	F	07/08/75	5	Hypsarrhythmia	Cryptogenic	A Rh+	A1, 2, B8, Bw15, Cw1
5	F	27/05/75	7	Hypsarrhythmia	Neonatal asphyxia	—	A3, Aw19, B14, Bw17
6	M	30/06/75	8	Hypsarrhythmia	Cryptogenic	A Rh+	A2, 3, Bw15, 40, Cw3
7	M	10/11/75	4	Hypsarrhythmia	Cryptogenic	A Rh+	A2, 9, B5, Bw21
8	F	25/08/75	7	Modified hyps.	Cryptogenic	—	A3, Aw23, B12, Bw40, Cw3,4
9	F	30/12/75	5	Modified hyps.	Cryptogenic	—	A2, 3, Bw15, B407, Cw3
10	M	27/01/76	4	Hypsarrhythmia	Neonatal asphyxia	—	A2, Aw23, B8, 12, Cw4
11	F	22/01/76	5	Hypsarrhythmia	Neonatal asphyxia	A Rh+	A11. Aw19, B12, Bw40, Cw3
12	M	29/12/75	6	Hypsarrhythmia	Neonatal asphyxia	A Rh+	A1, Aw24, B7, Bw15, Cw3
13	M	15/12/75	5	Hypsarrhythmia	Cryptogenic	—	A2, B7, Bw21
14	M	02/04/75	16	Hypsarrhythmia	Neonatal asphyxia	B Rh+	A2, 3, B7, Bw15, Cw3
15	F	05/02/76	6	Hypsarrhythmia	Neonatal asphyxia	—	A1, 3, B7,8
16	F	11/10/75	4	Severely abnormal	Cryptogenic	O Rh+	A2, Aw19, Bw40, Cw3
17	F	14/01/76	9	Hypsarrhythmia	Neonatal meningitis	A Rh−	A1, 28, B5, Bw40, Cw3
18	M	13/07/76	3	Hypsarrhythmia	Cryptogenic	—	A1, 3, B18, Bw17, Cw5
19	F	05/08/75	8	Severely abnormal	Neonatal asphyxia	O Rh+	A3, 28, B7, 12
20	M	16/04/76	4	Hypsarrhythmia	Cryptogenic	A Rh+	A1, Aw32, B7, 12
21	M	03/02/76	4	Hypsarrhythmia	Neonatal asphyxia	—	—

Summary

21 new cases of infantile spasms were reported in 1976 from paediatric departments in Denmark. The connection between infantile spasms and the Lennox-Gastaut syndrome is mentioned, because of reports of a significantly higher incidence of HLA-B7 in children with Lennox-Gastaut syndrome. The HLA antigen distribution in 19 of the 21 children was compared with that of 1967 healthy adults. No difference in the HLA antigens was demonstrated between children with infantile spasms and controls, whether in the material as a whole, or in the cryptogenic or symptomatic groups. However HLA typing of children with infantile spasms should continue in the search for a potential genetic marker in this grave disease, particularly in view of the reported high incidence of HLA-B7 in children with the Lennox-Gastaut syndrome.

Table 2 *HLA antigen frequency in 19 patients with infantile spasms and 1967 controls (from the tissue-typing laboratory)*

Infantile spasms (19 patients)		*Controls (1967)*
HLA antigen	%	%
HLA-A1	36·8	31·1
HLA-A2	42·1	53·6
HLA-A3	42·1	26·9
HLA-A9	5·3	17·3
HLA-A10	0·0	9·6
HLA-A11	5·3	10·1
HLA-A28	10·5	10·0
HLA-Aw19	21·0	17·8
HLA-Aw23	10·5	—
HLA-Aw24	15·8	—
HLA-Aw32	5·3	—
HLA-B5	10·5	10·6
HLA-B7	31·6	26·8
HLA-B8	15·8	23·7
HLA-B12	36·8	25·2
HLA-B13	0·0	4·3
HLA-B14	5·3	4·5
HLA-B18	5·3	7·1
HLA-B27	0·0	8·6
HLA-Bw15	26·3	17·9
HLA-Bw16	0·0	5·4
HLA-Bw17	10·5	7·7
HLA-Bw21	10·5	3·5
HLA-Bw22	0·0	3·8
HLA-Bw35	0·0	13·1
HLA-Bw40	26·3	17·9
HLA-B407	5·3	—
HLA-Cw1	5·3	8·4
HLA-Cw2	0·0	11·0
HLA-Cw3	47·4	37·0
HLA-Cw4	10·5	17·1
HLA-Cw5	5·3	—

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Familial neurodegenerative disorder associated with raised urinary vanillylmandelic acid

Urinary vanillylmandelic acid (VMA) is often raised in children with neuroblastoma (Voorhess and Gardner, 1962). It is sometimes transiently raised in infants in heart failure, after surgery, exchange transfusion, or during an acute asthmatic attack (Hakulinen, 1971).

Hirschberger and Kleinberg (1976) reported failure to thrive in an infant who had persistently raised urinary levels of VMA and in whom no neural crest tumour was found at necropsy. We report a child with a neurodegenerative disorder in whom hypertension and persistently raised urinary VMA were noted.

Case report

A 9-month-old baby boy was referred with a history of developmental delay and a possible neurodegenerative disorder. He is the third child of healthy, unrelated parents.

The baby's sister died at $2\frac{1}{2}$ years. She had been well until 7-months old, and then regressed. During the next year she became progressively more spastic, had recurrent bouts of vomiting, and at 2 years required tube feeding. At this time episodes of eye rolling, fever, and profuse sweating were noticed during which she emitted an offensive aroma. She died in coma at $2\frac{1}{2}$ years. No necropsy was performed, and regrettably there is no information about her blood pressure. There is a healthy male sibling aged $3\frac{1}{2}$ years.

Our patient had been well until 6 months when he began to show signs of regression with delayed milestones. He was noted to have brief cyanotic episodes, during which he would stiffen, sweat profusely, and emit a musty smell similar to his sister. During the next 9 months frequent short generalised convulsions were noted. Sweating continued and during the summer months he often required rehydration in hospital.

When examined at 9 months his height, weight, and head circumference were all around the 10th centile. Socially he was very responsive. The cranial nerves were normal but limbs were hypertonic with brisk reflexes. He had poor head control with marked head lag on pulling to sit, and he was unable to sit unsupported. The liver and spleen were just palpable. His blood pressure was consistently raised at 120/80 mmHg, with paroxysms of up to 180/110, often associated with intense irritability and sweating.

Examination at 18 months showed evidence of further regression. His liver remained just palpable and his blood pressure was persistently raised with a diastolic of 90–95 mmHg.

On a low tyramine diet, introduced because of the similarity of some of the clinical features of this syndrome to those occurring in adverse reactions to monoamine oxidase inhibitors, his neurological status remained virtually unchanged, with fewer episodes of irritability and paroxysmal hypertension. There was no further regression.

Investigations

Routine haematology and biochemistry, blood ammonia, creatine phosphokinase, copper, zinc, renin and aldosterone, and white cell lysosomal enzymes were all normal. There were no vacuoles in the lymphocytes, no abnormal storage cells in bone marrow, and no metachromatic granules in the urine. Examination of urine for amino and organic acids failed to show any consistent abnormality. Loading diets of leucine, isoleucine, and valine had no effect clinically or biochemically. ECG showed left ventricular hypertrophy although the chest *x*-ray was normal.

A skeletal survey showed generalised demineralisation with a possible compression fracture in the