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Movement disorders in Japanese encephalitis

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Abstract Movement disorders in Japanese encephalitis (JE), although reported, have not been analyzed systematically. In this study, we report an analysis of movement disorders in 14 out of 17 JE patients, correlated with the radiological findings. All patients had at least a four fold rise of IgG antibodies against JE in a haemagglutination inhibition test. The patients' ages ranged between 2 and 54 years and 4 of them were women. Extrapyramidal signs, such as hypokinesia, hypophonia and masking of the face, were present in all patients by the first month as the patients came out of the coma – except for 1 patient. Eight patients had axial and 3 tongue dyskinesia; rigidity was present in 6 and tremor in 2 patients. At 3 months, these symptoms improved considerably in 6 patients. Cranial CT scan revealed thalamic involvement in 10, which was bilateral in 9 patients. Two patients had brain stem and one had cerebellar involvement. Cranial MRI was carried out in 9 patients and revealed additional findings in lentiform nucleus, midbrain and pons in 3 each and cerebellum in 4 patients. Bilateral thalamic involvement on MRI was seen in all the patients, including two patients whose CT scans were normal. SPECT studies using ^{99m}Tc-ECD revealed bilateral thalamic hypoperfusion in all (n = 7) and frontal hypoperfusion in 3 patients. In JE, movement disorders are common and may be due to thalamic involvement in isolation or in combination with basal ganglia or midbrain or both.

Key words Movement disorder · Encephalitis · Japanese encephalitis · Thalamus

Introduction

Extrapyramidal syndromes are recognized as a sequelae of a number of acute viral encephalitides, including Japanese encephalitis, Western equine encephalitis, central European tick-born encephalitis, polio, Coxsackie B, measles, vericella zoster and encephalitis lethargica [5, 8, 13]. Japanese encephalitis is the commonest human epidemic encephalitis in the world and continues to be an important health problem in India, China, Thailand, Burma and Nepal [9, 12]. A systematic analysis of the frequency, pattern and evolution of the movement disorders in JE, however, has not been reported. We have noticed a high frequency of thalamic involvement in CT and MRI in Japanese encephalitis [11]. Thalamus is responsible for relaying various sensory and motor stimuli that can influence the motor functions as well. A recent meta-analysis of behavioural and motor consequences of focal lesions of basal ganglia has drawn attention to the anatomical basis of different movement disorders [4]. In this communication we report an analysis of movement disorders in Japanese encephalitis patients and discuss these in the light of the radiological findings.

Patients and methods

Seventeen patients with JE who were confirmed by an at least fourfold rise of lgG titres in the convalscent sera, employing the haemagglutination inhibition (HI) test have been included in this study. Five of these patients were seen in 1993 (nos. 1–5) and were included in an earlier report on radiological and neurophysiological changes in JE [11]; 6 patients (nos. 6–11) were seen in 1994 and the remainder in the year 1995. The neurological findings were recorded on admission, 1 month and 3 months after the onset of illness. The neurological assessment included the Glasgow Coma Scale, muscle power, tone, tendon reflexes and sensations. Extrapyramidal signs such as hypokinesia, hypophonia, masking of the face, rigidity, dystonia, dyskinesia, tremor and other abnormal movements were also noted. Hypokinesia, masking of the face, hypophonia, rigidity and tremor were graded 0–4 following scores of the Unified Parkinson's Disease Rating Scale [6] and dystonia also following the dystonia scale described by Fahn [7] on a 0–4 scale (0 = normal, 1 = slight, 2 = moderate, 3 = severe and 4 = marked). The minimental scale was used to assess mentation when the patient was able to cooperate. Cranial CT scan was carried out in 12 patients on admission, employing a whole-body third-generation CT scanner (W400 Hitachi, Japan) with a display matrix of 512×512 and spatial resolution of 3 mm at 0.5 contrast. The scan time for each slice was 4.5 s; 10-mm plain and contrast axial sections were taken parallel to the orbitomeatal line. Cranial MRI was carried out on a 1.5 T scanner (Magnetom 22614 SP, Siemens AG, Germany) using a circularly polarized head coil and T1, and T2 and proton-density-weighted spin-echo sequences.

SPECT studies for regional cerebral blood flow were carried out employing a head tome (Shimadzu Japan) using ^{99m}Tc-labelled ethyl cystine dimer (ECD). The patient was positioned in the gantry and 20 mCi of ^{99}Tc-ECD IV was injected in an antecubital vein. Three rims of dedicated high-resolution detectors obtained simultaneous slices of the brain. An on-line computer coupled with the system received the data and reconstructed the images.

Patients 1–4 were followed up for 2 years, nos. 6–11 for 1 year and the remainder for 3 months. Recovery was defined as poor at the end of 3 months if the patient was bedridden, as partial if the patient needed help for daily activities and complete if no help was needed for such activities [11].

Results

Movement disorders were present in 14 out of 17 JE patients; of the remaining 3 patients, 2 died during the acute stage and 1 had no movement disorder. The age of the patients included in this study ranged between 2 and 54 years and 4 were women. All patients presented with fever and altered sensorium. Consciousness started improving by 4 weeks in all except 1 patient (range 1–6 weeks). All patients were mute, had masking of the face and prominant slowing of purposeful movements. Eight patients had axial dystonia, which was associated with retrocollis in 4. Involuntary recurrent tongue protrusion was present in 3 patients in the 1st month, which subsided by the 3rd month and was replaced by jaw-opening dystonia in 1 (no. 6). Severe rigidity was present in 6 and tremor of the hands in 2.

At the 3-month follow-up, the symptoms of hypokinesia, hypophonia and masking of the face improved considerably in 6 patients. In these patients the speech volume was low and the speech output reduced. These patients walked slowly with short steps and had poor arm swing. Axial dystonia improved in 4; tremor, however, had completely disappeared at the 3-month follow-up in both patients (patients 1 and 14). Rigidity did not improve in any patient except 1 (patient 6). The pattern and time course of movement disorders were quite variable. Movement disorders were noted as the patient's consciousness improved. The mean time of appearance of movement disorders was 28 (15–45) days after the onset of illness. The movement disorders persisted for 1–3 weeks and then gradually reduced in the majority of patients. It was interesting to note that tremor and chorea regressed earlier (1–2 weeks), whereas other movement disorders such as rigidity, hypokinesia, hypophonia, dystonia and masking of the face were more protracted and persisted in some patients. The variation in the time course of different movement disorders was best illustrated in patient 6. On regaining consciousness after 3 weeks, this 10-year-old girl started having opisthotonus and rapid protrusion and retraction of the tongue along with akinesia, masking of the face and mutism. Tongue dyskinesia subsided after 2 weeks; however, she developed jaw-opening dystonia. At 3 months, hypokinesia, masking of the face, rigidity and trunk dystonia were markedly reduced, but hypophonia persisted. The details of different movement disorders and their 3-month follow-up are presented in Table 1. Minimental assessment was possible at 1 month in 2 patients. The score of the minimental scale was 24 and 28, respectively. At 3 months, 5 patients were able to cooperate for the test, and the score ranged between 28 and 30. The remaining 7 patients were severely abulic. One patient had delayed recovery from the coma, and at 8 months her minimental scale score was 30, although she had masking of the face (patient 4). The cutcome at the end of 3 months was poor in 7, partial in 4 and complete in 3 patients.

Four of the 5 patients who were examined in 1993 were periodically evaluated at 3-month intervals for 2 years. Movement disorders were not present in any of these 4 patients after 1 year, although 1 patient had cerebellar signs (no. 4) and in another patient the deficits were blindness and seizures, which were controlled with antiepileptic drugs (no. 3). Of the patients who developed encephalitis in 1994 (patients 7–11), 4 of them were on regular follow-up for 1 year. One patient had minimal left-sided rigidity and poor arm swing (patient 9). Two patients had complete recovery from movement disorders (nos. 10, 11). One patient had persistent disability, rigidity hypokinesia, masking of the face, hypophonia and dystonia (patient 8). The patient who had jaw-opening dystonia at 3 months improved considerably from hypokinesia, hypophonia, truncal dystonia and masking of the face; however, she was still unable to close her mouth (patient 6).

Table 1 Extrapyramidal signs and radiological findings in Japanese encephalitis patients (*I* initial examination, 1 month, *F* final examination, 3 months, *BL* bilateral, *ND* not done)

Patient[a] No.	Age (years)	Hypokinesia		Masking		Rigidity		Dystonia		Hypophonia		Areas involved other than thalamus	SPECT (hypoperfusion)
		I	F	I	F	I	F	I	F	I	F		
1	28	4	1	4	1	0	0	0	0	4	1	Mid-brain[b]	ND
2	15	4	1	4	1	0	0	0	0	4	1	Mid-brain, pons, cerebellum[b]	ND
3	2	4	2	2	0	0	0	0	0	4	2	Cerebellum[b]	ND
4	54	4	4	3	3	0	0	0	0	3	3	Pons[b]	ND
5	18	4	4	3	3	4	4	4	4	4	4	BL lentiform nucleus, cerebellum[b]	ND
6	10	4	2	3	2	3	0	4	2	4	4	Mid-brain[b]	ND
7	6	4	4	3	3	4	4	4	4	4	4	–	ND
8	44	4	4	3	3	4	4	4	4	4	4	–	BL thalamic and left frontal
9	12	4	2	4	2	0	0	3	2	4	2	–	BL thalamic
10	50	4	1	4	2	0	0	0	0	4	1	–	BL thalamic
11	14	4	2	3	2	0	0	4	0	4	2	–	BL thalamic and left frontal
12	13	4	3	4	3	4	3	4	3	4	3	Lentiform nucelus, mid-brain[b]	BL thalamic and left frontal
13	17	4	4	4	4	0	0	0	0	4	4	Left cerebellum[b]	BL thalamic
14	10	4	3	4	3	4	3	3	2	4	3	Lentiform and pons[b]	BL thalamic

[a] Patients 1–6 and 12–14 are based on MRI and 7–11 on CT scan
[b] Based on MRI findings

Radiological findings

A cranial CT scan was carried out in 12 patients and revealed thalamic hypodensity in 10; the remaining 2 patients had a normal CT scan; MRI of both these patients, however, revealed thalamic involvement, showing mixed intensity lesion on both T1 and T2. The thalamic changes on CT scan were bilateral in all except the one who had right-sided hypodensity with a small area of haemorrhage. On cranial CT scan, brain-stem involvement was present in 2: left cerebellar, pons and midbrain involvement in 1 patient each. The mid-brain lesion was located on the left side, involving crus cerebri and substantia nigra. MRI studies were possible in 9 patients, which revealed bilateral thalamic involvement of mixed intensity on T1 and T2, suggestive of haemorrhage (Fig. 1). MRI revealed additional involvement of lentiform nucleus in 3, mid-brain in 3, pons in 3 and cerebellum in 4 patients. These lesions were hypointense on T1 and hyperintense on T2 except for the cortical and pontine lesions in 1 patient each, which were hyperintense on both T1 and T2 sequences.

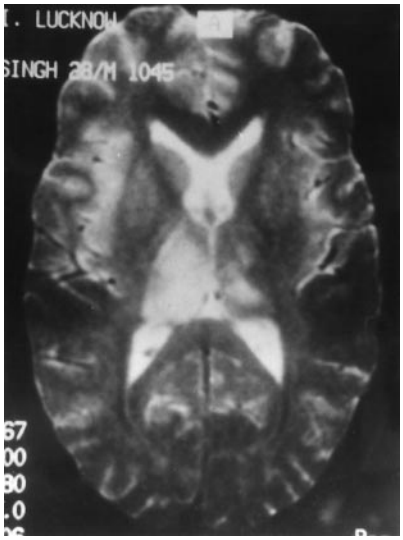

Fig. 1 Cranial MR scan axial cut of a patient with Japanese encephalitis in T2 sequence showing bilateral lesion in thalamus (patient 1)

Clinico-radiological correlation

Hypokinesia, hypophonia and masking of the face, which were present in all patients, were associated with bilateral thalamic involvement on imaging. Out of 4 patients with pronounced rigidity, MRI revealed changes in lentiform nucleus in 3 patients and the mid-brain in another besides bilateral thalamic involvement. Axial dystonia was present in 8 patients, in whom extrathalamic abnormalities were present in 3 patients, including bilateral lentiform nucleus changes on MRI in 2 and pontine in 1. In the remaining 5 patients with dystonia, no MR scan was possible.

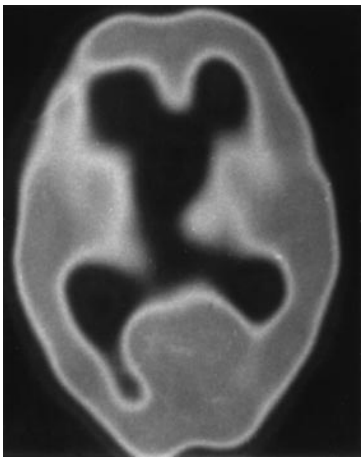

Fig. 2 SPECT study of a Japanese encephalitis patient who had bilateral thalamic and left frontal hypoperfusion (no. 8). She had pronounced rigidity, hypokinesia, masking of the face and hypophonia; CT scan revealed bilateral thalamic involvement

A cranial CT scan of the patient with jaw-opening dystonia revealed mid-brain involvement in addition to thalamic lesions. Transient tremor was present in 2 patients, 1 of whom had right mid-brain involvement. The various movement disorders and radiological changes are shown in Table 1. The extent of brain involvement on imaging did not correlate with the outcome. A patient with extensive bilateral involvement of the thalamus, mid-brain, pons and cerebral cortex improved completely (no. 2).

SPECT studies in 7 patients, carried out after 3 months, revealed bilateral thalamic hypoperfusion in all and frontal hypoperfusion in 3 patients (Fig. 2). Blood flow in the other areas of the brain was normal.

Discussion

Masking of the face, hypophonia and profound bradykinesia were characteristically noted in 14 out of 17 patients with Japanese encephalitis as their consciousness improved. This clinical picture was reminiscent of parkinsonism. Parkinsonism can be seen in the lesions of nigrostrial pathways. Such lesions can be in the nigra or striatum or both. Loss of dopaminergic innervation of the corpus striatum in turn disinhibits the medial globus pallidus via direct and indirect striatopallidal pathways. Fibres from the globus go to the dorsolateral thalamus, which then relay to cerebral cortex for programming of motor movement [4]. In our study the mid-brain was involved in 4 patients (bilaterally in 2 and unilaterally in 2) and globus pallidus in 3. In the remaining 7 patients, however, there was no radiological evidence of pallidal or mid-brain involvement. In our patients without any mid-brain or pallidal involvement, the parkinsonian features could be due to thalamic involvement. The important role of thalamus in relaying the basal ganglionic inputs to motor cortex is well known. It is interesting to note that in a meta-analysis of thalamic lesions, parkinsonian features were observed very rarely [10]. The rarity of parkinsonism in thalamic lesions, mainly following strokes, may be due to restricted thalamic involvement of corresponding vascular territory. In encephalitis, the thalamic involvement may be more diffuse, affecting several thalamic nuclei and their connections, which may account for the above-mentioned parkinsonian features. In the meta-analysis of thalamic lesions, only occasional reports of resting tremor were found. In the present study, 2 patients had resting tremor, which was restricted to one arm in 1 and the tongue and arm in the other. These patients had mid-brain and lentiform nucleus involvement, respectively, on MRI. The tremor in both patients was transient, as reported in thalamic lesions [10].

Dystonia was found in 8 patients with JE. This was mostly axial and of the fixed type. In thalamic lesions, dystonia has been reported in 16 out of 33 patients whose lesions were restricted to the thalamus. All of the JE patients with dystonia had bilateral thalamic lesions. MRI studies were possible in three patients with dystonia and thalamic involvement on CT. In these patients the lentiform nucleus was found to be involved bilaterally. Dystonia commonly occurs in lentiform nucleus involvement, particularly the putamen [14]. In JE, dystonia is possible because of both thalamic or thalamic and lentiform nucleus involvement. Dystonia following thalamic strokes has been reported after 1–9 months, whereas in JE it has generally been noted by 1 month as the patients recover from coma; dystonia tended to decrease thereafter in 4 patients.

Another striking feature in our patients was pronounced abulia at 1 month. Abulia is attributed to the involvement of the prefrontal cortex-caudate-pallido-thalamocortical circuit [1, 2]. In our patients neither caudate nucleus nor prefrontal cortex was involved on CT or MRI, although the involvement of dorsolateral prefrontal cortex or caudate nucleus is commonly associated with abulia [4]. Thalamic involvement, however, could account for these symptoms by affecting the above mentioned circuits. In 2 of our patients with a profound rigid, akinetic and abulic state, SPECT studies not only revealed bilateral thalamic hypoperfusion, but left frontal hypoperfusion as well, which was present 3 months after the ictus. In view of the normal cerebral cortex on CT scan, cortical hypoperfusion may be due to cerebral dyschiasis. Cerebral dyschiasis is commonly described with vascular insult and is attributed to anterograde Wallarian degeneration, retrograde degeneration, trans-synaptic degeneration of cortical neurons, or reduced functional activity of cortical neurons without actual degeneration [3]. The latter mechanism seems to be more likely in our patients. Most of these symptoms improved at the 3–month follow-up in all except 7 patients who were severely ill and did not re-

cover. The correlation of movement disorders in JE patients with the radiological changes suggests an important role of the thalamus and its connections. In our study, MRI was carried out in 9 patients only, and in 6 patients both CT and MRI scans were done. MRI revealed additional findings, which were not seen on CT scan in any except 1 patient. MRI studies, therefore, are more useful in studies on the anatomical basis of movement disorders; however, it was not the primary aim of our study.

From this study, we conclude that in Japanese encephalitis, many movement disorders are commonly encountered as the patient recovers from coma. These movement disorders are generally transient or have a regressive course. In view of the common involvement of thalamus in JE, thalamus may have an important role in isolation or in combination with basal ganglia or midbrain involvement.

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