Original Article

Movement disorders of probable infectious origin

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Abstract

Background: Movement disorders (MDs) associated with infections remains an important debilitating disorder in the Asian countries. **Objectives:** The objective of the following study is to report the clinical and imaging profile of a large cohort of patients with MDs probably associated with infection. **Materials and Methods:** This was a chart review of 35 patients (F:M-15:20) presenting with MD in the Neurology services of National Institute of Mental Health and Neurosciences, India. The demographic profile, type of infection, time from infection to MD, phenomenology of MD and magnetic resonance imaging (MRI) findings were reviewed. **Results:** The mean age at presentation was 22.6 ± 13.3 years, (5-60), age of onset of MD was 15.7 ± 15 years, and duration of symptoms was 6.9 ± 8.1 years (42 days to 32 years). The mean latency of onset of MD after the infection was 5.9 ± 4.2 weeks. The phenomenology of MD were: (1) Pure dystonia-28.6%, (2) dystonia with choreoathetosis-22.9%, (3) Parkinsonism-14.6%, (4) pure tremor, hemiballismus, myoclonus and chorea-2.9% each, and (5) mixed MD-22.9%. Most often the MD was generalized (60%), followed by right upper limb (31.4%) and left upper limb (8.6%). A viral encephalitic type of neuroinfection was the most common infection (85.7%), which was associated with MD. Abnormalities of brain MRI, seen in 79.2%, included signal changes in (1) thalamus-52.0%, (2) putamen and subcortical white matter-16% each, (3) pons-12%, (4) striatopallidum, striatum and grey matter-8% each, and (5) caudate, cerebellum, lentiform nucleus, midbrain and subthalamic nucleus-4.0% each. **Conclusions:** MDs associated with infection were the most often post-encephalitic. Dystonia was the most common MD, and thalamus was the most common anatomical site involved.

Key Words

Dystonia, myoclonus, neuroinfection, secondary movement disorders, tremor parkinsonism

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Introduction

Movement disorders (MD) can be classified as "primary," which are a manifestation of an underlying neurodegenerative disorder, or "secondary" to a wide range of neurological or systemic diseases. Various etiological factors have been described causing secondary MDs (SMDs) such as cerebrovascular disease,[1] space occupying lesions, trauma and infections. Netravathi *et al*.[2] in their study had reported infectious causes representing up to 20.4% of all SMDs.[2] MDs secondary to infectious causes are diverse ranging from hypokinetic disorders such as parkinsonism (PAR)[3,4] to hyperkinetic disorders such as chorea,[5,6] dystonia,[7] tics,[5] tremor and myoclonus (MYO). Various pathogenic organisms have been known to cause SMDs.[3-5,7] Viral organisms such as HIV[4] have been reported causing whole range of MDs. Kalita and Misra[8] in their study on Japanese encephalitis had reported predominant post-encephalitic dystonia. Isolated case reports of influenza virus encephalitis causing chorea and paroxysmal dyskinesias have also been reported.[6,9] Bacterial infections such as streptococcal group causing Sydenham's chorea have been most widely proven. Though the incidence of Sydenham's chorea has reduced it is still prevalent in developing countries. Parasitic infections such as toxoplasma abscesses in the subthalamic nucleus, thalamus, caudate nucleus, or globus pallidus have been reported to be associated with contralateral limb ballism, choreoathetosis, and dystonia.[3]

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Several studies have attempted to explain the MDs secondary to specific infectious agent. Apart from a large study on SMD[2] conducted at our center, most of the reports are limited to a single patient or a series of patients defining a particular infectious agent. The conclusions from these studies are varied and difficult to generalize. The objectives of our study were to

1. Characterize the pattern (phenomenology) of MD temporarily related to infection
2. Characterize the probable nature of infection causing SMD, and

(3) Correlate the phenomenology of abnormal movements with the type of infection, clinical and imaging characteristics of the patients.

Materials and Methods

A retrospective chart review of patients with SMD associated with infection, evaluated at the National Institute of Mental Health and Neurosciences, Bangalore, India was performed. A total of 35 patients (F:M-15:20) with a mean age at presentation of 22.6 ± 13.3 years from 2007 to 2012 were recruited for the study. The primary inclusion criteria were patients presenting with MDs, where definite temporal relationship with a probable infectious insult could be attributed to cause the MD. The demographic profile, type of infection, time from infection to MD, phenomenology of MD and magnetic resonance imaging (MRI) findings were reviewed. Phenomenology of MD secondary to infectious cause were clinically categorized into:

1. Pure dystonia (DYS),
2. Pure tremor (TRM),
3. Pure MYO,
4. PAR,
5. Dystonia plus (DYS+), which consisted of dystonia with choreoathetosis,
6. Predominant tremor with dystonia,
7. Hemiballismus (HMB)
8. Chorea (CHOR), and
9. Mixed SMD (MIX), which included a combination of any of the above categories.

Table 1: Demographic, clinical and imaging profile of 35 patients with MDs probably related to infection

Age	Sex	AAO-MD (years)	Duration (years)	Latency of infection (weeks)	IBPA	MD	MRI (signal changes)
13	Female	11	2	48	Gen	DYS	CAU
45	Male	44	0.1	4	Gen	PAR	GM, WM
9	Female	6	3	12	RUL	Mixed	GP
27	Male	27	0.1	1	Gen	PAR	GP
27	Male	24	3	2	LUL	PAR	GP, PUT
23	Female	12	11	1	LUL	DYS	LEN
32	Male	25	7	6	RUL	DYS	N
16	Female	7	9	2	Gen	DYS+	N
19	Female	10	9	2	RUL	DYS+	N
7	Male	7	0.5	4	Gen	DYS+	N
11	Female	8	3	12	RUL	DYS+	N
11	Male	11	0.5	2	Gen	DYS+	N
60	Female	60	0.1	1	Gen	Mixed	N
58	Female	58	0.1	1	Gen	Mixed	N
28	Male	12	16	8	Gen	CHOR	N
38	Female	38	0.5	1	Gen	Mixed	N
13	Male	7	6	4	Gen	DYS	PUT
23	Female	0.75	22	1	Gen	DYS+	PUT
10	Male	10	0.5	2	LUL	DYS+	PUT, MB
29	Male	29	0.1	1	Gen	PAR	SP
12	Male	8	4	8	Gen	DYS+	SP, THA, MB
9	Male	8	1	4	RUL	Mixed	STR
18	Female	7	11	3	Gen	DYS	THA
25	Male	1	24	4	RUL	DYS	THA
25	Male	5	20	4	RUL	DYS	THA
24	Male	14	10	36	Gen	Mixed	THA
42	Male	10	32	8	RUL	HMB	THA
13	Male	11	2	1	RUL	TRM	THA
22	Female	22	0.1	1	Gen	PAR	THA, Ce
5	Male	3	2	4	Gen	DYS	THA, PO
16	Female	6	10	4	RUL	Mixed	THA, PO
14	Male	7	7	6	RUL	Mixed	THA, SN
15	Female	7	8	2	Gen	DYS	THA, ST, GM, WM
21	Male	4	17	3	Gen	MYO	THA, WM
31	Female	31	0.5	2	Gen	DYS	WM

AAO = Age of onset, CAU = Caudate, CHOR = Chorea, Ce = Cerebellum, DYS = Pure dystonia, DYS+ = Dystonia plus, Gen = Generalized involvement, GM = Grey matter, GP = Globuspallidus, HMB = Hemiballismus, IBPA = Initial body part affected, LEN- Lenticulate, LUL = Left upper limb, MD = Movement disorder present, MB = Mid-brain, MIX = Mixed SMD, MYO = myoclonus, N = Normal, PAR = Parkinsonism, PO = Pons, PUT = Putamen, RUL = Right upper limb, SP = Striatopallidum, SN = Substantianigra, STR = Striatum, ST- subthalamus, THA = Thalamus, TRM = pure tremor, WM = White matter, MRI = Magnetic resonance imaging, SMD = Secondary movement disorders

All patients underwent an MRI scan of the brain. Statistical analysis included descriptive statistics.

Results

A total of 35 patients were recruited in the study, after fulfilling the criteria. The demographic details of these patients are summarized in Table 1. Majority of patients were admitted in the neurology ward, either from the casualty and emergency services or from the outpatient clinics. All patients were evaluated by a single MD specialist. Patients who presented with acute neuroinfection, underwent all relevant investigations to establish the nature of neuroinfection. Serological tests and cerebrospinal fluid analysis were performed when indicated; however, the extent of these investigations depended on the availability in our hospital and affordability of the patients. All patients suspected of herpes simplex encephalitis underwent electroencephalography. MRI of the brain was performed for each patient, sometimes under general anesthesia.

Type of MDs

Table 2 shows the predominant phenomenology of the MDs in the patients. The latency from the insult to the onset of SMD was 5.9 weeks. DYS was the most common phenomenology present in 10 patients (28.6%), followed by DYS+ choreoathetosis and a mixed SMD (22.9% each). PAR was present is 5 patients (14.6%). One patient each had TRM, MYO, HMB and chorea.

Type of probable infection

Twenty patients (57.1%) came to our center for evaluation and management of their MD by MD specialist and were already evaluated and treated for their neuroinfection in an outside hospital. The rest 15 patients (42.9%) were evaluated in our center for their infection and later for their MDs.

A final diagnosis of probable encephalitis based on clinical features (fever with altered sensorium or loss of consciousness, with or without seizures) and available laboratory tests and MRI were made in 30 patients (85.7%). Among the rest, one patient with history of fever, behavioral changes and PAR was found to have neurosyphilis, two had a clinical profile suggestive of opsoclonus-MYO syndrome (one had dengue confirmed by positive serum IgM for dengue), and the rest two patients had febrile illness where no specific etiology could be found. None of the patients who were tested for were HIV positive. No one had neurocysticercosis or was on treatment for tuberculosis prior to the current illness. Clinical and available laboratory details of the patients are given in Table 3.

Table 2: Profile of MDs

Profile of MDs	No. (percentage)
Dystonia+choreoathethosis	8 (22.9)
Mixed	8 (22.9)
Pure dystonia	10 (28.6)
Parkinsonism	5 (14.6)
Pure tremor	1 (2.9)
Hemiballismus	1 (2.9)
Myoclonus	1 (2.9)
Chorea	1 (2.9)

MDs = Movement disorders

MRI findings

Abnormalities of brain MRI were seen in 25 patients (79.2%) [Table 4]. Thalamic signal changes were predominantly seen in 13 patients (52%). Signal intensities in other structures such as caudate, cerebellum, lentiform nucleus, midbrain, and subthalamic nucleus were observed in one patient each (4.0%) [Table 4]. Representative MRI findings of three patients are given in Figures 1-3.

Subgroup analysis

We divided the patients into three groups according the age of insult (probable neuroinfection): (a) Group A: ≤6 years, (b) Group B: >6 to ≤25 years, and (c) Group C: >25 years [Table 5]. This division into groups based on age of insult is similar to a study by Scott and Jankovic[10] who had studied the latency of different MDs following static brain injury.

1. There was a significant difference in the duration of the disease between the three groups with patients in group A having maximum duration of illness followed by group B and group C (A: 14.0 + 9.0 years; B: 6.7 + 7.41 years; C: 1.0 + 2.4 years; A vs. B: $P = 0.004$; A vs. C: $P = 0.002$)
2. There was no significant difference in the latency of onset of SMD after the initial insult between the three groups
3. The prevalence of dystonia (DYS and DYS+) among the three groups was: 57.6% (four patients) in Group A, 60% (12 patients) in group B and 25% (two patients) in group C. These differences were not statistically significant
4. In these groups, among those with dystonia (either DYS or DYS+), MRI showed signal changes in the thalamus in three out of the four patients (75%) in group A, compared to three out of the 12 patients (25%) in group B and was none among the two patients in group C. These differences were not statistically significant
5. Among all patients with SMD in the three groups, the prevalence of MRI signal changes in the thalamus was significantly higher in group A compared with group C (71.4% vs. 0%; $P = 0.01$) and also higher in group B compared to group C (40% vs. 0%; $P = 0.03$).

Discussion

SMD related to infectious etiology consist of both, hyperkinetic and hypokinetic extrapyramidal manifestations, which results from insult to the basal ganglia. They are diverse and different from their idiopathic counterpart not only in their clinical presentation but also in their natural history, prognosis and treatment.[3] Most of the published literature on SMD related to infection emphasize on a particular microbial agent and the MDs related to that agent. There is no published paper, which characterizes the pattern of these SMDs due to infections. Therefore, our study, which was done in a large tertiary care neurology referral center, attempted to explore the clinical and neuroimaging characteristics of SMDs due to infection.

In our study, DYS was presenting feature in 10 patients (28.6%) and DYS+ choreathetosis in eight patients (22.9%). Overall dystonia (DYS and DYS+) was present in nearly 18 patients (51.5%). Comparing the prevalence of dystonia in different groups based on age at the insult, in the

Table 3: Details of infection

History s/o infection					CSF					Hospital	Final clinical diagnosis*
Fever	Headache	AS/LOC	Sz	Others	JE	HSV	VDRL	HIV	Others		
+		+								O	E
+	+	+			−	−	−	−		N	E
+		+	+		−	−	−	−		N	E
+										O	Febrile illness, ? Etiology
+		+			−	−	−			N	E
+		+	+							O	E
+		+			−	−				N	E
+		+								O	E
+		+			−					O	E
+		+								O	E
+		+	+							O	E
+		+	+		−	−		−		N	E
+		+	+							O	Febrile illness, ? Etiology
+				Jaundice					HBsAg +	O	OMS
+		+								O	E
+		+		Diarrhea						O	E
+		+			−	−			Widal +	N	E
+		+	+							O	E
+		+	+							O	E
+		+			−	−		−		N	E
+		+								N	E
+		+				−		−		N	E
+		+	+	Rash						O	E
+		+								O	E
+		+	+		−	−				N	E
+			+		−					O	E
+		+				−	−			N	E
+	+					−				N	E
	+			Behavior changes			+			N	Neurosyphilis
+		+								O	E
+		+			−	−				N	E
+		+	+							O	E
+		+								O	E
+	+			Rash					Dengue IgM+	N	OMS
+		+	+							O	E

*Final diagnosis after the patients was evaluated at NIMHANS. AS = Altered sensorium, E = Encephalitis, HIV = Human immunodeficiency virus, HSV = Herpes simplex virus, JE = Japanese encephalitis, LOC = Loss of consciousness, N = Evaluated in NIMHANS, O = Evaluated outside NIMHANS, OMS = Opsoclonus myoclonus syndrome, Sz = Seizure, VDRL = Veneral disease research laboratory, CSF = Cerebrospinal fluid, NIMHANS = National Institute of Mental Health and Neuro Sciences, HBsAg: Hepatitis B surface antigen, IgM = Immunoglobulin M

age group ≤6 years, dystonia was present in four patients (57.6%), in >6 to ≤25 years in 12 (60%) and in >25 years in two (25%) patients. Kalita *et al*.[11] in their study on Japanese encephalitis of 67 patients had found dystonia to be commoner in children (<15 years of age) (20 patients 66.7%) compared to adults (>15 years of age) (seven patients 18.6%). Basumatary *et al*.[12] in their study of 148 Japanese encephalitis patients had also found dystonia to be commoner in children (<14 years of age) (19 patients 43.1%) compared to adults (>14 years of age) (19 patients 18.2%). In our study on MRI, signal changes were seen in the thalamus in three (75%) out of the four patients with dystonia in the age group <6 years compared to the other groups in which thalamus was involved in three (25%) out of the 12 patients with dystonia in >6 to <25 years and not involved in >25 years of age patients. There was no significant correlation with the presence of dystonia and thalamic involvement on MRI in any of these three groups. Our finding differs from that of Basumatary *et al*.[12] had shown the presence of thalamic lesion in computed tomography/MRI had a significant relationship to the development of dystonia in children. This could be due to the fact that they divided their sample size into two groups adult and children compared to ours in which groups were divided according to the age of insult. Secondly, Basumatary *et al*.[12] had only recruited diagnosed cases of Japanese encephalitis compared with ours where we were studying general para and post-encephalitis MDs.

In our study of 35 patients, history suggestive of encephalitis (fever with altered sensorium with or without seizures) was the most common presentation in 30 (85.7%) patients. DYS was the most common presentation, 10 patients (33.3%), in patients with history of encephalitis. In India Japanese encephalitis remains one of the most common causes of post-encephalitic MDs.[13] Misra and Kalita[13] in their study of 209 patients on the spectrum of MDs with encephalitis had reported 74 patients to have MDs. Parkinsonian features were present in 36 (48.6%), dystonia in six (8.1%) and both in 32 patients (43.3%).

Table 4: Imaging characteristics of the patients with abnormal MRI

Signal changes in	No. (percentage)
Thalamus	13 (52)
Putamen	4 (16)
Subcortical white matter	4 (16)
Pons	3 (12)
Striopallidal	2 (8)
Striatal	2 (8)
Grey matter	2 (8)
Caudate	1 (4)
Cerebellum	1 (4)
Lentiform	1 (4)
Mid brain	1 (4)
Subthalamus	1 (4)

MRI = Magnetic resonance imaging

Table 5: Clinical characteristics according to the age of insult

Parameters	<6 years	>6 to <25 years	>25 years	*P* value
No. of patients	7	20	8	
Mean AAO of MD	3.67±2.1	10.67±4.2	39±13.9	
Duration of illness	14±9	6.7±7.41	1±2.4	0.004
Latency of the infection	4.57±3.4	7.8±12.22	2.13±1.8	0.35

AAO = Age of onset, MD = Movement disorder

In our study, two patients had a history of fever for about 10 days followed by history of opsoclonus and MYO. Many viral disorders have been reported in literature as the cause of opsoclonus and MYO. Morita *et al*.[14] had reported of a patient with influenza virus infection with opsoclonus MYO after a period of 1 week of fever. Verma *et al*.[15] in their study of 26 patients of diagnosed Dengue infection had reported two patients with opsoclonus MYO syndrome. Many isolated case reports have been published reporting opsoclonus MYO syndrome in adults due to mycoplasma pneumonia infection.[16-19]

Limitations

The major limitation of our study was the failure to identify the infectious etiology by laboratory tests in many patients. This is partly attributed to the delay of many patients in consulting our hospital, inability to afford costly investigations, and finally lack of facilities to diagnose uncommon viral infections.

Conclusions

Encephalitis is the most common cause for SMD due to infection with dystonia being the most common MD. Age of insult plays an important role in the presence of the type of MD with dystonia being a much more commoner finding in patients with younger age of insult. A larger follow-up study is needed in these patients to look into the pattern of MDs in different age groups and pathophysiology behind it. Thalamus is the most common involved structure on MRI in younger age of insult groups, but there is no correlation in the presence of dystonia in patients with thalamus involvement in all the three groups.

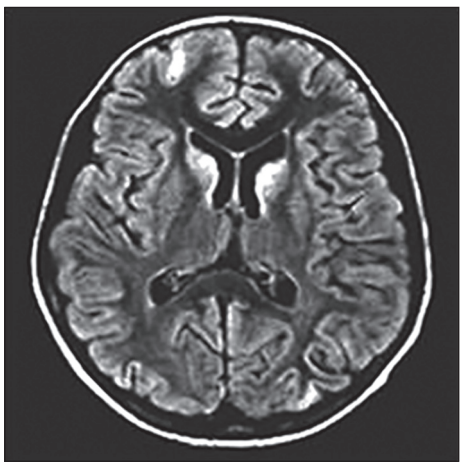

Figure 1: T2 weight fluid attenuated inversion recovery magnetic resonance imaging (MRI) of a 13-year-old girl who had history of high-grade fever, headache and loss of consciousness 2 years back and later developed generalized dystonia. MRI shows hyperintensities in bilateral caudate, left posterior parietal and right frontal grey matter

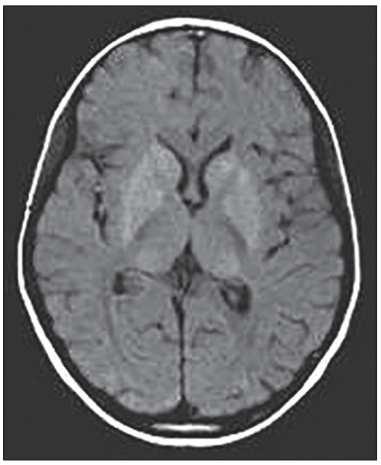

Figure 2: T1 weight magnetic resonance imaging (MRI) of a 27-year-old man who had a history of high grade fever with unconsciousness 3 years back, followed by symmetric Parkinsonism. MRI shows hyperintensities in bilateral caudate, globus pallidi, putamen and thalami

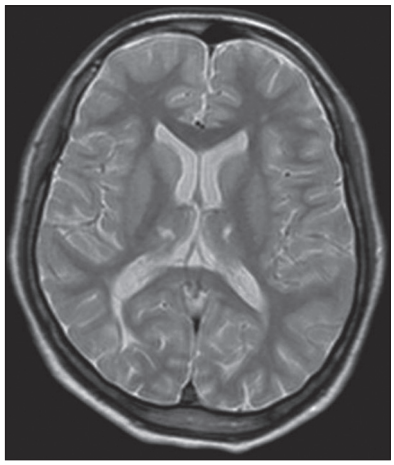

Figure 3: T2 weight magnetic resonance imaging (MRI) of a 16-year-old girl who had a history of high grade fever, with seizures associated with unconsciousness 10 years back, who later presented with upper limb dystonia and choreoathetoid movements years. MRI shows hyperintensities in bilateral thalami

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