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Seizure Semiology and Neuroimaging Findings in Patients with Midline Spikes

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Summary: *Purpose:* Midline epileptiform discharges are rare compared with discharges at other scalp locations. Neuroimaging results and semiologic seizure characteristics of patients with midline spikes are not adequately described. The aim of this study was to describe the neuroimaging findings and detailed seizure semiologies in patients with midline spikes.

Methods: We reviewed the EEG database of the University of Michigan Medical Center and identified 35 patients with midline spikes. Information about seizure types and neuroimaging results was obtained from a review of medical records. The seizures were classified according to the International League Against Epilepsy (ILAE) criteria and semiologic classification.

Results: Twenty-nine (83%) patients had a history of seizures. Complex partial seizures and simple partial seizures were the most common seizure types, experienced by 66% of patients. The age at seizure onset was within the first 10 years in 90% of patients. According to the semiologic seizure classification, automotor seizures and tonic seizures were the most common seizure types. Neuroimaging studies were abnormal in 45% of patients. When focal abnormalities were detected, they were lateralized to one of the frontal lobes in all cases.

Conclusions: Our results indicate that in the majority of patients, midline spikes represent focal epileptiform activity rather than fragments of generalized discharges, and are most commonly associated with seizures of partial onset. Automotor seizures and tonic seizures are the most common semiologies. Focal radiologic abnormalities tend to be lateralized to one of the frontal lobes. **Key Words:** Midline spikes—Semiologic seizure classification—Neuroimaging—Frontal lobe—Tonic seizures.

Epileptiform discharges localized to the midline vertex are relatively uncommon compared with discharges at other scalp electrode sites. They were reported mostly in children, and were most commonly associated with generalized tonic–clonic seizures (1–4). The majority of previous studies was small and predominantly focused on EEG characteristics and clinical findings (1,2,5). One larger study also addressed the prognosis of patients with midline spikes (6). The neuroimaging findings and semiologic characteristics of patients with midline epileptiform activity have not yet been adequately described. The aim of this study was to describe the neuroimaging findings and semiologic seizure classification in patients with midline spikes.

MATERIALS AND METHODS

From a total of ~20,000 EEGs performed over a 10-year period from 1990 to 2000, we identified 35 records that had midline spikes as their only epileptiform abnormality. Midline spikes were defined as focal epileptiform discharges localized to, or of highest amplitude at one of the vertex scalp electrodes Fz, Cz, or Pz. Midline spikes were differentiated from spiky vertex waves by their occurrence during wakefulness in all patients. We excluded neonatal patients and patients with additional generalized or focal epileptiform discharges. All EEGs were performed by using 21-channel recordings with electrodes placed according to the International 10-20 system, and both referential and bipolar montages were used. Routine activation procedures such as intermittent photic stimulation and hyperventilation were performed when not contraindicated. The patient's medical records were reviewed to obtain information regarding age at seizure onset, seizure types, and results of neuroimaging. A neuroradiologist (D.G.H.) blinded to the clinical data independently reviewed all available imaging studies. Imaging protocols varied from routine screening to high-resolution epilepsy-focused studies.

We confirmed the seizure semiologies for the majority of patients by telephoning the patients, family members, or their legal guardians. The seizure classification was made according to the International League Against Epi-

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lepsy (ILAE) criteria (7). The semiologic seizure classification was made according to the classification system introduced by Lüders et al. (8). This classification is based solely on the clinical symptomatology and describes evolution of the seizure sequences independent of the EEG, neuroimaging, and historical information (8). The χ^2 test was used for group comparisons. All statistically significant results were set at p values of <0.05.

RESULTS

Demographics

Of the 35, 18 (51.5%) were male patients. The age at the time of the EEG ranged between 18 months and 38 years (mean, 11.8 years). Twenty-nine (83%) of the 35 patients had seizures. In those patients, the mean age at seizure onset was 5.1 years and ranged from birth in two patients to age 37 years in one patient. The seizure onset was in the first 5 years of life in 22 (76%) of the 29 patients and in the first 10 years in 26 (90%) of the patients. The remaining six patients were referred for reasons other than seizures, including breath-holding spells, temper tantrums, and a neurodegenerative disorder. There was no gender difference in the group of patients without seizures. Three of those patients were older than 10 years, whereas the other three were between ages 2 and 5 years. Mental status was normal in 22 (63%) patients, and 13 (37%) patients were diagnosed with mild to moderate mental retardation.

EEG abnormalities

Midline spikes were strictly localized to one or two midline electrodes in 20 (57%) patients and were of maximal amplitude at one or two midline electrodes with a field distribution to the adjacent electrode(s) in 15 (43%) patients. The spikes were localized or of highest amplitude at the Cz electrode site in 20 (57%; Fig. 1), at Fz in eight (23%), at Pz in five (14%), and equipotential at Fz and Cz in two (6%) patients. There was no significant difference between the topographic location of the spike and occurrence of seizures. All of our patients had midline epileptiform abnormalities during wakefulness. Sleep activated the frequency of the midline epileptiform discharges in 12 (67%) of 18 patients. Intermittent photic stimulation had no effect on spike frequency. In 14 (40%) patients, there were additional nonepileptiform abnormalities on the EEGs, including slowing of the posterior background in nine, focal parasagittal slowing in two, generalized continuous slowing in two, intermittent rhythmic delta activity in two, and bitemporal slowing in one patient.

Seizure classification

The majority of patients with midline spikes and epilepsy had seizures of partial onset. According to the ILAE classification, 14 (48%) of 29 had complex partial seizures with or without secondary generalization (eight had complex partial seizures only, and six had complex partial seizures with occasional generalization). Five (17%) of 29 had simple partial seizures; in four patients, it was the only seizure type (with either tonic or clonic motor components in all patients, associated with autonomic and visual aura in one patient each) and in one patient, the seizure occasionally secondarily generalized. Three (11%) patients had generalized tonic–clonic seizures that could not be stratified as to whether they were primary or secondarily generalized seizures. Seven patients (24%), when classified according to the ILAE had generalized seizures that consisted of tonic seizures in four, atonic seizures in two (associated with generalized tonic–clonic seizures in one patient) and myoclonic seizures in one patient.

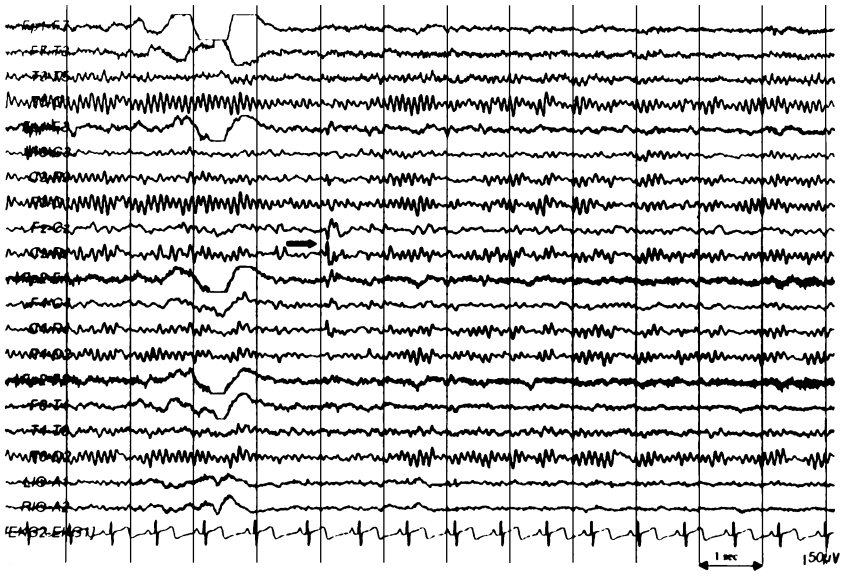

FIG. 1. EEG of a midline spike with maximal amplitude at the Cz electrode site (arrow) in an 11-year-old patient.

TABLE 1. *Clinical and EEG characteristics of patients with midline spikes*

Patient no.	Gender	Age (yr)	Age at seizure onset (yr)	Site of midline spike	Seizure classification (ILAE)	Semiologic seizure classification
1	F	5	4	Pz	Tonic	Bilateral tonic
2	M	2.5	2	Pz	CPS	Automotor
3	F	3	3	Pz	CPS	Automotor
4	F	37	37	Fz	GTCS	Tonic–clonic
5	M	2	1	Fz > Cz	Tonic	Bilateral tonic → right arm clonic
6	M	9	3	Cz > C4	SPS	Autonomic aura → left leg tonic
7	F	5	4.5	Cz	GTCS	Tonic–clonic
8	M	7	6	Cz	SPS	Right arm tonic
9	M	30	21	Cz	Atonic with occasional GTCS	Atonic → tonic–clonic
10	F	6	4	Cz	CPS	Automotor
11	F	10	10	Cz	CPS	Automotor
12	M	3	1	Cz	CPS with secondary GTCS	Automotor → tonic–clonic
13	F	21	0.5	Cz	GTCS	Tonic–clonic
14	M	4	0.1	Cz > C3 or C4	CPS	Automotor
15	M	27	6	Cz	Tonic	Bilateral tonic
16	M	7	3	Cz > C4	Atonic	Atonic
17	M	1.5	1	Fz > F3, F4	Myoclonic	Generalized myoclonic
18	M	38	Birth	Fz > F3, F4	Tonic	Bilateral tonic
19	F	10	1.5	Fz > F3	CPS with secondary GTCS	Automotor → tonic–clonic
20	M	29	Birth	Fz > F3	CPS with secondary GTCS	Automotor → tonic–clonic
21	F	4	3.5	Fz	CPS	Left arm clonic → Automotor
22	F	31	1.5	Fz	CPS with secondary GTCS	Automotor → tonic–clonic
23	M	4	2	Cz	CPS with secondary GTCS	Automotor → tonic–clonic
24	F	2	2	Cz > Fz, Pz	CPS	Left arm tonic → Automotor
25	M	4	4	Cz > C4	SPS	Left leg clonic
26	F	19	4	Cz > C3, C4	SPS	Asymmetric tonic → right arm clonic
27	M	30	14	Cz > C4	SPS with occasional GTCS	Visual aura → left leg tonic → tonic–clonic
28	F	2	2	Fz, Cz	CPS with secondary GTCS	Automotor → tonic–clonic
29	F	8	6	Pz > P4	CPS	Automotor
30	M	11	—	Cz	No seizure	—
31	M	5	—	Pz	No seizure	—
32	M	2	—	Cz	No seizure	—
33	F	2	—	Cz	No seizure	—
34	F	19	—	Cz, Fz > C3, C4	No seizure	—
35	F	13	—	Cz > C3, C4	No seizure	—

GTCS, generalized tonic–clonic seizure; SPS, simple partial seizure; CPS, complex partial seizure.

When classified according to the semiologic classification (8), 14 (48%) patients had automotor seizures, all of which were classified above as complex partial seizures. An automotor seizure is defined as one with complex motor behavior consisting of automatisms involving the distal segments of hands, feet, mouth, or tongue (8). In two of those patients, the automotor seizures were preceded by clonic jerking of the left upper extremity in one and tonic extension of the left arm in the other. Six of the automotor seizures were occasionally followed by generalized tonic–clonic seizures. Eight (27%) patients had tonic seizures as their main seizure component. The tonic activity was bilateral in four patients, focal in three patients, and asymmetric in one patient. Two patients had

TABLE 2. *Radiologic findings in patients with midline spikes*

Patient no.	MRI findings
1	NI
2	—
3	NI
4	Right frontal encephalomalacia involving the entire lobe; bilateral white-matter changes in both frontal lobes (post radiation)
5	Diffuse brain volume loss
6	Cortical thickening in the right superior frontal gyrus (paramidline)
7	Punctate white-matter signal abnormalities, no focal abnormalies
8	NI
9	NI
10	Few cortical asymmetries without signal abnormalities, most prominent in the left dorsolateral frontal lobe
11	NI (CT)
12	NI
13	NI
14	NI
15	Diffuse brain volume loss
16	Left frontal shunt, bilateral dysmorphic occipital lobes, thin corpus callosum posteriorly
17	—
18	—
19	Right frontal encephalomalacia
20	—
21	Right frontal encephalomalacia involving inferior frontal and orbitofrontal regions
22	Cerebellar atrophy
23	NI
24	—
25	NI
26	Area of cortical asymmetry and blurring of the gray–white matter interface in the left SMA
27	Area of possible cortical thickening in the left middle frontal gyrus
28	NI
29	NI
30	—
31	NI
32	NI
33	NI
34	NI
35	Diffuse brain volume loss

All patients had brain MRIs except for patient # 11, who underwent a head CT scan.
NI, normal imaging.

right upper extremity clonic jerking at the end of their tonic seizure. Two of the focal tonic seizures were preceded by an autonomic and a visual aura, respectively. Three (10%) patients had tonic–clonic seizures, two (7%) had atonic seizures (one occasionally followed by tonic–clonic seizure), one (4%) had myoclonic seizures, and one patient (4%) had focal clonic seizures. A detailed description of the seizure sequences is shown in Table 1.

Neuroimaging studies

A total of 29 patients had a radiologic study, including brain magnetic resonance images (MRIs) in 28 and a head computed tomography (CT) scan in one patient (Table 2). The neuroimaging findings were abnormal in 13 (45%) patients. Six patients had diffuse cerebral abnormalities with no associated focal abnormalities, consisting of diffuse cerebral and cerebellar atrophy in three, and dysmorphic occipital lobes associated with a thin corpus callosum, cerebellar atrophy, and white-matter signal changes in one patient each. Seven (24%) patients had focal neuroimaging abnormalities, lateralized to one of the frontal lobes in all cases. Three patients with focal frontal abnormalities had right-sided encephalomalacia, and the remaining four patients had subtle or prominent cortical abnormalities in either frontal lobe (Figs. 2 and 3). For patients with midline spikes and seizures, there was a significant correlation ($p = 0.04$) between presence of MRI findings and partial-onset and/or generalized tonic–clonic seizures (Table 3). There were no significant differences between the electrode site of maximal discharge and the mean age of patients, seizure type, or presence of a neuroimaging abnormality.

DISCUSSION

Unlike other studies that described the clinical, EEG characteristics (1–4) or prognosis (6) of patients with midline spikes, we also evaluated seizure semiologies and neuroimaging findings. In contrast to other studies that reported generalized tonic–clonic seizures as the most common seizure type (1–4), our results indicate that midline spikes are most commonly associated with seizures of partial onset. In our series, 66% of patients had simple partial or complex partial seizures with occasional secondarily generalized tonic–clonic seizures. Complex partial seizures, which were experienced by 48% of the patients in our study, were reported in only 0 to 10% of previous series (1–4,). Less rigorous descriptions of seizure semiology and less stringent criteria for defining midline spikes with the inclusion of the records containing additional epileptiform discharges in previous studies could partly explain those differences (1–4). Our findings were consistent with those of Bagdorf and Lee (6), who excluded patients with additional epileptiform abnormalities and who reported complex partial seizures as the most common seizure type, experienced by 50% of patients in their series. The semiologic features of seizures in patients with midline spikes were not previously reported. In our series, we found that all patients with complex partial seizures had automotor seizures, a semiology most frequently associated with temporal lobe epilepsy or with spread to the temporal lobes (9). Because isolated midline spikes are extremely rare in patients with temporal lobe epilepsy, the automotor seizures could, in some patients, be related to temporal lobe propagation from an extratemporal epileptogenic region. For instance, seizures of cingulate gyrus origin were

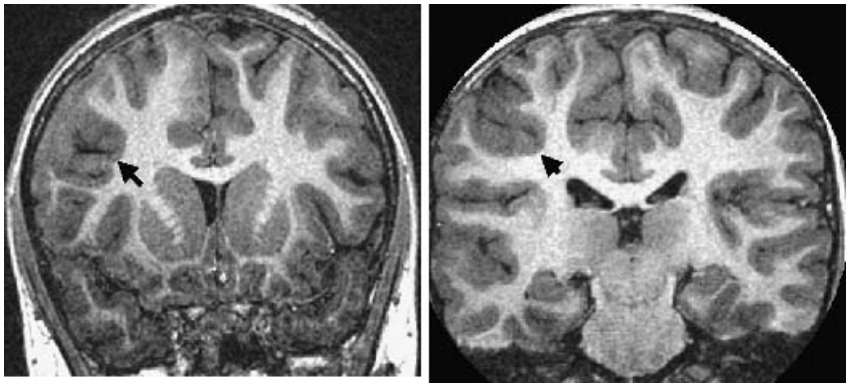

FIG. 2. Coronal imaging using thin-section fast spoiled-gradient sequence of a patient demonstrating areas of cortical thickening in the inferior frontal gyrus (arrow) in the right anterior **(A)** and posterior **(B)** frontal lobe.

found to propagate to the medial temporal lobe and manifest as complex partial seizures (10,11). Tonic motor seizures were the second most common seizure. This finding is not surprising because these seizures usually originate from the supplementary sensorimotor area and the premotor region (12), with the interictal epileptiform discharges frequently localized or maximal at the vertex. All of our patients with simple partial seizures had a motor component, either clonic or tonic, suggestive of paracentral or premotor frontal lobe origin or propagation. These results support that at least for the majority of patients, midline spikes are focal in origin (2,5,6) and do not represent fragments of generalized discharges (1,3).

Neuroimaging findings in patients with midline spikes were briefly reported in two previous studies (6,13). Bagdorf and Lee (6) reported that head CT scans were abnormal in 37% of cases, with brain MRIs being performed in only three patients. Molaie (13) described the CT findings of nine patients and reported various degrees of cerebral atrophy and ventricular enlargement without focal abnormalities. In our study, the neuroimaging studies were abnormal in 52% of patients with midline spikes and seizures. In these patients, the abnormalities were diffuse in 42% and focal in 58% of patients. When focal abnormalities were detected, they were localized to one of the frontal lobes in all cases, especially over the dorsolateral or mesial surfaces. Although this would suggest a frontal lobe seizure origin for those cases, it can be confirmed only by noninvasive/invasive ictal monitoring and/or by findings on substraction ictal single-photon emission computed tomography (SPECT) (14). The localization of focal abnormalities on neuroimaging signifies that in patients with midline spikes, one must pay special attention to abnormalities in the frontal lobes. This is especially important for patients with medically refractory partial epilepsy, who could be candidates for epilepsy surgery. With the continued improvement in the sensitivity of high-resolution MRI, it is likely that future neuroimaging studies in patients with midline spikes will report a higher frequency of abnormalities.

The clinical and electroencephalographic findings in our study are consistent with previously reported results in patients with midline spikes. We found that isolated midline spikes are most commonly seen in children, are associated with seizures in the majority of cases, with onset of seizures typically occurring in the first decade of life. Although the high association between midline spikes and seizures could partly reflect the referral pattern to our institution, previous studies reported a frequency of seizures ranging from 71 to 91% in patients with midline spikes (1–4,6). Although midline spikes were of highest amplitude at the midline vertex (Cz electrode site) in the majority of cases, the discharges were localized and isolated to the frontal (Fz electrode site) or parietal vertex (Pz electrode site) in some patients. These results are concordant with previous studies that have

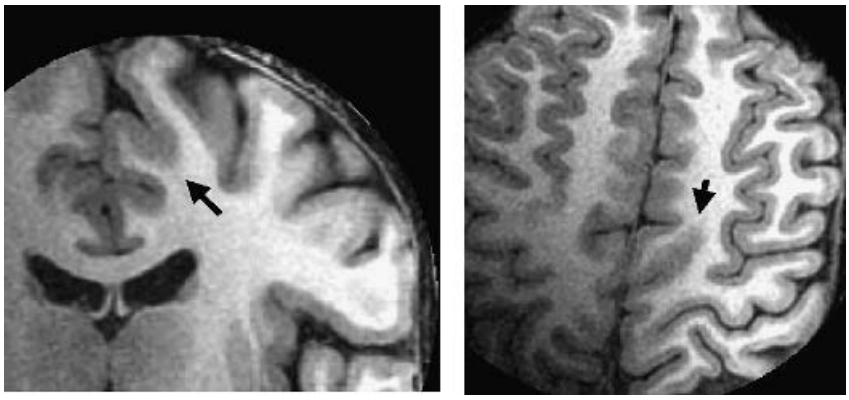

FIG. 3. Coronal **(A)** and axial **(B)** imaging with a fast spoiled-gradient sequence of a patient demonstrating blurring of the gray–white matter interface in the posterior frontal cortex (arrow), also involving part of the supplementary motor area.

TABLE 3. *Seizure characteristics and MRI findings*

	Frontal abnormality	Generalized abnormalities	Normal MRI
Partial onset and/or generalized tonic–clonic seizures	7	2	10
Generalized seizures	0	3	2
No seizures	0	1	4

MRI, magnetic resonance imaging.

documented similar findings (1–3,6). There were no significant differences between the electrode site of maximal discharge and the mean age of patients, seizure type, or presence of a neuroimaging abnormality. From the results of our study and those of prior studies, it is possible to start defining the electroclinical syndrome of midline spikes. Electroencephalographically, the findings consist of spikes localized or of highest amplitude at the vertex (Fz, Cz, or Pz), with the discharge localized to or of highest amplitude at the Cz electrode site in the majority of cases. The discharges are activated by sleep and occasionally seen only during sleep. The EEG background can be normal or can show focal or diffuse abnormalities. There is a strong association with seizures, with onset in the first decade in the majority of patients. Although virtually every seizure type has been described in patients with midline spikes, the majority will have complex partial seizures, simple partial seizures with a motor component, or generalized tonic–clonic seizures. Neuroimaging will be normal, focally abnormal, or diffusely abnormal. When focal, the abnormalities are most commonly seen in the frontal lobes.

The better to define the electroclinical syndrome, future studies should evaluate ictal EEG findings and substraction ictal SPECT in patients with midline spikes, to delineate whether some of the seizures that appear generalized at onset, such as tonic and atonic seizures, could be of frontal lobe origin (15). In addition, it would be interesting to evaluate prospectively the longitudinal changes of midline spikes in terms of their location and whether they represent a persistent or a transitory age-related phenomenon.

In summary, midline spikes are frequently seen in children, often maximal at Cz, and in the majority of patients represent focal epileptiform activity rather than fragments of generalized discharges. Seizures of partial onset are the most commonly associated seizure type and focal imaging abnormality, when present, abnormalities usually involve one of the frontal lobes.

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