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PRESENILIN-1 MUTATION ASSOCIATED WITH AMNESIA, ATAXIA, AND MEDIAL TEMPORAL LOBE T2 SIGNAL CHANGES

In the correct clinical context, an important cause of medial temporal MRI signal abnormality is herpes simplex encephalitis. In more subacute presentations, autoimmune or paraneoplastic limbic encephalitis are common etiologies. We present a man with subacute onset of memory impairment and gait ataxia whose MRI was suggestive of limbic encephalitis. After exclusion of infectious causes, immunosuppression was started. He eventually proved to have Alzheimer disease (AD) due to the S170F mutation in the presenilin 1 (PS-1) gene.

Case report. A 34-year-old welder presented to our neurology department with memory impairment and unsteadiness. His work colleagues reported a few months' history of frequently losing his tools and difficulties with his balance.

When examined he was disorientated in time and he had no recall of a name and address after a 5-minute delay. There was head titubation, truncal, mild finger-nose, and gait ataxia. Diadochokinesis was poor bilaterally. Otherwise the examination was normal.

MRI showed generalized cerebral (figure e-1 on the *Neurology*[®] Web site at www.neurology.org) and cerebellar atrophy, increased signal from both hippocampi and amygdalae (axial proton density, figure 1, figure e-2), but no gadolinium enhancement.

Full autoimmune screening including voltage-gated potassium channel antibodies, CSF examination (opening pressure 18 cm, protein 365 g/dL, glucose 4.9 mmol/L [serum 9.2 mmol/L], white cells 2, red cells 6, cytology, oligoclonal bands, immunoglobulin G index, herpes simplex virus, varicella zoster virus, enterovirus, and Whipples PCR, protein 14–3-3), paraneoplastic antibodies (anti-amphiphysin, anti-Hu, -Ri, -Yo, -PNMA antibodies), tumor markers, testicular ultrasound, and whole-body CT and PET were normal or negative. The EEG showed frequent bursts of slow activity maximally in the temporal regions with an alternating emphasis and occasional sharp waves and spikes.

Figure 1 Axial proton density MRI of the brain at presentation, demonstrating bilateral mesial temporal hyperintensity (arrows) and generalized atrophy

Prednisolone (nonproprietary) and phenytoin (nonproprietary) were initiated.

The patient's balance improved but his memory remained impaired. During the first 2 years, his Mini-Mental State Examination score was stable at 24/30 (losing points on recall and orientation) but then dropped to 10/30 (losing additional points on serial 7s, language tasks, and drawing) within a 6-month period when he also suffered increasing unsteadiness, myoclonus, and frequent seizures.

Pulsed cyclophosphamide (nonproprietary) was started.

Three months later, he was readmitted with severe dysarthria, becoming increasingly aggressive and bedbound with frequent upper limb myoclonic jerks, increased tone globally, brisk reflexes, bilateral ankle clonus, and equivocal plantar responses.

MRI scan revealed worsening atrophy particularly of the mesial temporal lobes and some high signal within the hippocampi. After extensive negative investigations, a brain biopsy from the nondominant frontal lobe was performed. Microscopic examination of conventional hematoxylin & eosin–stained preparations revealed no obvious abnormality (figure e-3). There were no abnormal cellular infiltrates, no spongiosis, and no significant neuronal loss. Cotton-wool plaques were not seen. Immunohistochemistry,

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however, revealed abundant A β -peptide deposition, mostly as diffuse plaques with some cored plaques (figure e-4). Amyloid angiopathy was not a feature. Immunohistochemistry to abnormally phosphorylated tau, using the AT8 antibody, revealed neurofibrillary tangles, neuropil threads, and neuritic plaques (figures e-5 and e-6). No α -synuclein pathology was detected. CD68 revealed an upregulation of microglia, in places in clumps presumed to be associated with plaques. Genetic testing of the PS-1 gene identified the S170F mutation. Both parents (father aged 73 and mother aged 68) are alive with no neurologic problems. The patient has no siblings. There is no history of any neurologic illness in the grandparents but their age at death is unavailable.

Discussion. AD can cause rapidly progressive dementia and ataxia. We are unaware of any descriptions of AD causing MRI signal change suggestive of limbic encephalitis. There is a large body of evidence of distinctive atrophy patterns in AD.¹ In patients with PS-1 mutations, prominent MRI white matter hyperintense lesions² and fluid-attenuated inversion recovery hyperintense signal in the anterior subependymal region of the splenium³ have also been reported.

The S170F mutation is a single base pair substitution in exon 6 at codon 170 of the PS1 gene causing an amino acid change from serine (TCT) to phenylalanine (TTT). It was first reported in 2 patients presenting with progressive forgetfulness aged 26 and 27. The index case had myoclonus, generalized seizures, brisk reflexes, and rigidity. No neuroimaging procedures were reported.⁴ The other 2 S170F cases reported in the literature showed generalized and more focal temporal lobe atrophy on MRI.^{5,6} In our case the clinical features as well as the atrophy and signal abnormality in the medial temporal lobes on MRI scanning could have been entirely in keeping with paraneoplastic or immune-mediated limbic encephalitis.⁷ The 2-year interval of relative stability on immunosuppressive treatment could be indicative of an underlying inflam-

matory component in what is otherwise thought to be a genetic degenerative condition.

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A DISTINCTIVE SEIZURE TYPE IN PATIENTS WITH *CDKL5* MUTATIONS: HYPERMOTOR-TONIC-SPASMS SEQUENCE

Recent recognition of the encephalopathy associated with *CDKL5* (cyclin-dependent kinase-like 5) mutations has led to molecular diagnosis in affected girls. A characteristic progressive 3 stage electroclinical epilepsy course occurs with onset by 3 months of age.^{1,2}

After we observed unusual prolonged seizures in a girl with *CDKL5* mutations, we sought to determine

if *CDKL5* mutations were associated with a distinctive electroclinical seizure type.

Methods. We reviewed the video-EEG monitoring (VEM) and clinical details of all girls with *CDKL5* abnormalities recruited into our epilepsy genetics research studies.

Details of the molecular methods are described elsewhere.² In one subject a deletion of *CDKL5* was revealed by an Agilent aCGH 44K array and confirmed by quantitative PCR.

Table 1 Semiology and EEG findings in the hypermotor-tonic-spasms sequence

	Patient 1 (3 seizures)	Patient 2 (6 seizures)	Patient 3 (3 seizures)	Patient 4 (1 seizure ^a)
Age at recording	21 mo	4 y	6 mo	10 mo
Seizure phase				
Hypermotor				
Semiology	Truncal rotation, axial rocking, kicking of LL, minimal UL involvement, crying	LL kicking and truncal flexion	Wiggling of head, shoulders, and UL, more subtle than in other patients	Movements of limbs (discerned under blanket), vocalization
EEG	Diffuse delta (figure e-1a)	Bilateral rhythmic delta activity, phase reversing in midline, posterior predominance; low-voltage fast activity in frontocentral regions bilaterally	Diffuse delta activity with posterior maximum	Diffuse delta with anterior maximum (diffuse decrement and low voltage fast activity in frontocentral regions bilaterally 20 s before clinical onset)
Duration, s	20–60	10–15	10–20	10
Tonic				
Semiology	Symmetric extension of all limbs	Extension of all limbs, superimposed vibratory component, followed by unusual jittery hand movements bilaterally	Abduction of UL, flexion of LL (head and eye deviation to right and initial extension of right leg in some seizures)	Symmetric extension of all limbs
EEG	Diffuse decrement (figure e-1b)	Attenuation followed by rhythmic delta evolving to Cz spikes	Attenuation and low voltage fast activity in frontocentral regions bilaterally	Diffuse delta, then diffuse attenuation; intermixed midline frontocentral sharp slow waves
Duration, s	20–45	20–30	30–40	25
Spasms				
Semiology	Bilateral extensor, initially superimposed on tonic seizure and then continuing	Bilateral extensor (asymmetric left > right in one seizure), LL about 200 ms prior to UL	Bilateral extensor with abduction and elevation of UL and adduction of LL	Bilateral extensor
EEG	High-voltage sharp slow complexes with negative maximum at vertex followed by periods of attenuation (figure e-1c)	High-voltage sharp slow complexes with negative maximum at Cz followed by periods of attenuation, sometimes with admixed β activity	High-voltage sharp slow complexes maximal in frontocentral midline followed by diffuse attenuation	High-voltage sharp slow complexes with negative maximum in frontocentral midline followed by attenuation
Duration, min	10–15	1–6 clinical (EEG pattern only: 8–55)	2.5–6	6
EEG background	Normal	Mild slowing with bifrontal and independent left and right temporal IED	Normal with frequent bilateral, independent and midline frontal and central IED	Normal with independent bilateral hemispheric IED

Abbreviations: IED = interictal epileptiform discharges; LL = lower limb; UL = upper limb.

^a Three seizures captured but video was available for only one seizure.

Standard protocol approvals, registrations, and patient consents. The study was approved by the Human Research Ethics Committee of all participating institutions. Signed informed consent for study participation and publication of the videos was obtained from the participants' parents.

Results. Four of 5 girls with *CDKL5* mutations had the distinctive seizure type. The clinical and molecular details are reported (table e-1 on the *Neurology*[®] Web site at www.neurology.org, molecular data previously reported for patients 1, 3, and 4³). Table 1 describes the electroclinical features of the seizure type captured during VEM between 6 months and 4 years of age in each girl.

Hypermotor-tonic-spasms sequence. The seizures (videos 1–3 on the *Neurology*[®] Web site at www.neurology.org) started in all patients within 70 seconds of awaken-

ing from sleep. In 2 cases the arousal was triggered by an auditory stimulus. The first part of the seizure began with a hypermotor phase with rocking, kicking, and vocalization which lasted 10–60 seconds and was accompanied by diffuse delta (figure e-1). Low-voltage fast activity in the frontocentral regions bilaterally was present during or preceding the hypermotor phase in 2 girls.

Second, a tonic phase followed, either with extension of all limbs or extension of the upper limbs and flexion of the lower limbs lasting 20–45 seconds. The EEG showed attenuation with superimposed low-voltage fast activity in the frontocentral regions bilaterally in one.

Third, the seizure evolved to a series of extensor spasms which lasted 1–15 minutes. Spasms were accompanied by high-voltage sharp slow complexes maximum in the frontocentral midline followed by attenuation.

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The hypermotor-tonic-spasms sequence was an age-dependent phenomenon as it was not seen in patient 1 at 6 months, patient 4 at 4½ years, or patient 3 at 5½ years.

Patient 5 did not have this seizure type on history or during VEM. This 2-year-old girl had seizure onset at age 2 weeks with a de novo mutation in *CDKL5* (c.175C>T, p.R59X). Tonic seizures and spasms at 16 months were captured during VEM but tonic seizures were not preceded by a hypermotor phase nor were they followed by prolonged clusters of spasms.

Discussion. We describe 4 girls with *CDKL5* encephalopathy who presented with a distinctive seizure sequence. We observed the hypermotor-tonic-spasms sequence in 4/5 (80%) girls with *CDKL5* mutations. This finding is supported by the previous description of similar seizure semiology in a single patient with a *CDKL5* deletion.⁴

Seizures began with a hypermotor phase which evolved to a tonic phase with bilateral upper limb abduction and culminated in a series of extensor spasms lasting up to 15 minutes. Seizures started after arousal from sleep and were long, lasting 3.5–17 minutes.

The onset of the hypermotor-tonic-spasms sequence was between 3.5 and 13 months (median 7.5 months), which was 1.5 to 11 months after seizures first began. It was not present at 6 months in one girl and after 4 years in 2 girls, indicating an age-dependent seizure type starting during the second stage of *CDKL5* epileptic encephalopathy.¹

It is well-recognized that focal seizures can occur with clusters of spasms either prior to, during, or following a cluster of spasms.⁵ The ictal onset with hypermotor features and the low-voltage fast activity in the frontocentral regions provide evidence for frontal onset of the hypermotor-tonic-spasms sequence. Hypermotor attacks occur very infrequently in young children⁶ and pure extensor spasms are also uncommon.⁷ These features are seen in our patients and suggest a specific but unknown pathophysiologic mechanism caused by *CDKL5* dysfunction.

We conclude that the distinctive hypermotor-tonic-spasms sequence is a feature of *CDKL5* epileptic encephalopathy; however, it is unlikely to be either 100% sensitive or specific. We have found that history alone may lead the clinician to suspect this unusual seizure type and thus to consider the diagnosis of a *CDKL5* encephalopathy with important implications for clinical diagnosis.

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VENTRAL INTRASPINAL FLUID-FILLED COLLECTION SECONDARY TO CSF LEAK PRESENTING AS BIBRACHIAL AMYOTROPHY

MRI has identified a broader clinical spectrum of CSF leaks than what was initially recognized. Although headache, particularly orthostatic, is the most common manifestation, most patients display additional symptoms, and some have no headaches.^{1,2} Other manifestations include cochleovestibular and oculomotor disturbances, cognitive impairment, interscapular pain, and imbalance.^{1,2} This report draws attention to yet another manifestation of CSF leaks: segmental amyotrophy related to cervical cord compromise from an intraspinal ventral epidural fluid-filled collection in communication with the subarachnoid space. The 3 reported patients showed clinical improvement after dural defect repair; imaging resolution of the intraspinal fluid-filled collection was demonstrated in all.

Case reports. *Case 1.* A 48-year-old man presented with a 5-year history of progressive, bilateral, asymmetric, proximal greater than distal, upper limb atrophy and weakness. EMG demonstrated chronic neurogenic changes in the C4–C8 myotomes. MRI showed a ventral extradural intraspinal fluid-filled collection from C2 to L4 with posterior displacement and flattening of the cord from C3–C7 (figure, A1 and A2). A dural defect was identified on a dynamic CT myelogram at T12–L1 (figure, A3); this was surgically closed. At 6-month follow-up, significant clinical improvement was noted; this was accompanied by complete resolution of the imaging abnormality (figure, A4 and A5).

Case 2. A 40-year-old man presented with a 2-year history of progressive, asymmetric, upper limb atrophy and weakness. Three years prior to the onset of his weakness, he experienced daily holocephalic headaches for a month. EMG demonstrated chronic neurogenic changes in the cervical and upper thoracic myotomes. MRI showed a ventral epidural fluid-filled collection from C3–L1 (figure, B1 and B2). Dynamic CT myelogram identified a high-flow CSF leak from the ventral aspect of the spinal canal at T11–T12 (figure, B3). A failed targeted thoracic epidural blood patch was followed by surgical repair of the dural defect. At 4-month follow-up significant clinical improvement was noted; corresponding imaging showed resolution of the ventral fluid-filled collection (figure, B4 and B5).

Case 3. A 32-year-old man presented with a 10-year history of progressive, proximal greater than distal, right upper limb weakness and atrophy and a 4-month history of progressive distal left upper limb weakness and atrophy. For the preceding 8 years, he had been symptomatic with exertional headaches with an orthostatic component. MRI brain revealed brain

sag suspicious for intracranial hypotension. EMG showed chronic neurogenic changes in the C5–T1 myotomes. MRI of the cervical and thoracic spine showed a ventral epidural fluid-filled collection from C2–T12 (figure, C1 and C2). This had been noted 1 year prior also and had prompted a shunt placement from the cyst to the pleural space. Despite the shunt, the fluid-filled collection persisted. A dynamic CT myelogram showed a CSF leak arising from the left C4 nerve root sleeve (figure, C3). This was surgically repaired. MRI done 6 months after surgical repair showed resolution of the fluid collection (figure, C4). Coincident improvement in upper limb strength was noted.

Discussion. The 3 patients reported here presented with segmental muscular atrophy and chronic neurogenic changes likely related to dynamic spinal cord compromise from an intraspinal ventral extra-arachnoid fluid-filled collection. A dynamic CT myelogram identified the dural defect (communication site between the subarachnoid space and fluid-filled collection).³ In case 2 the dural defect was adjacent to a spiculated osteophyte. All underwent successful surgical repair of the CSF leak.

Extra-arachnoid fluid collections are common in spontaneous CSF leaks.^{1,2} These are often supratentorial and over the cerebral convexities but are also encountered at the spinal level and at times may exist as encapsulated collections of CSF connected with the spinal subarachnoid space.⁴ Such zones of extra-arachnoid fluid collection have been reported in patients with superficial siderosis, where presentations of progressive weakness mimicking amyotrophic lateral sclerosis have been described.⁵ A preexisting CSF leak in these cases is thought to play a causative role.^{6,7}

The association of focal spinal amyotrophy with a ventral epidural fluid collection secondary to a CSF leak with clinical and imaging improvement of symptoms after treatment of the CSF leak supports a causative relationship. A CT myelogram or a dynamic CT myelogram can localize the dural defect.³ Surgical repair of the CSF leak rather than targeted epidural blood patches is the preferred intervention. We propose that the segmental cervical amyotrophy observed in our patients is a consequence of chronic dynamic pressure upon the ventral cervical spinal cord by the encapsulated fluid collection. This mechanism may be similar to that observed in Hirayama disease wherein neck flexion causes forward displacement of the posterior dura leading to ventral cord compression and enlargement of the posterior epidural space. An additional explanation might be conduction block over a tethered motor root segment produced by dorsal cord displacement. Dural defect-related extra-arachnoid fluid-filled collections are a potentially treatable cause of anterior horn cell dis-

Figure Preoperative (A1, A2, B1, B2, C1, C2) and postoperative (A4, A5, B4, B5, C4) MRI and preoperative CT myelogram (A3, B3, C3) in case 1 (A1–A5), case 2 (B1–B5), and case 3 (C1–C4)

(A1–A5) (Case 1) Sagittal (A1, A2) and axial (inset in A1, A2) MRI of the cervical (A1) and thoracic (A2) spine from case 1 showing the ventral intraspinal fluid collection from C2 to L4 with posterior displacement and flattening of the cervical cord from C3 to C7; reformatted sagittal (A3) and axial (inset in A3) dynamic CT myelogram showing leak at the T12–L1 interspace. Sagittal (A4, A5) and axial (inset in A4, A5) cervical (A4) and thoracic (A5) spine MRIs 6 months after repair of the dural defect showing resolution of the intraspinal fluid collection. (B1–B5) (Case 2) Sagittal (B1, B2) and axial (inset in B1, B2) MRI of the cervical (B1) and thoracic (B2) spine showing the ventral intraspinal fluid collection from C3 to L1 with loculation (inset in B2); reformatted sagittal (B3) and axial (inset in B3) dynamic CT myelogram showing leak at the T11–T12 interspace. Sagittal (B4, B5) and axial (inset in B4, B5) cervical (B4) and thoracic (B5) spine MRI done 4 months after repair showing resolution of the ventral fluid collection. (C1–C4) (Case 3) Sagittal (C1, C2) and axial (inset in C1, C2) MRI of the cervical (C1) and thoracic (C2) spine showing the ventral intraspinal fluid collection from C2 to T12; axial cut from a dynamic CT myelogram (C3) showing leak from a left C4 nerve root cyst into an anterior extradural fluid collection. Sagittal (C4) and axial (inset in C4) cervical spine MRI 6 months after repair of the CSF leak showing resolution of the intraspinal fluid collection.

ease and should be included in the differential diagnosis of segmental amyotrophy.

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