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Focal brain dysfunction in a 41-year old man with familial alternating hemiplegia

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Abstract The acute pathophysiologic changes during hemiplegic spells and the long-term outcome of alternating hemiplegia remain obscure. In a 41-year-old male with familial alternating hemiplegia we found an increase in right frontal cerebral blood flow 3 h into a 5-h left hemiplegic episode. A repeat high-resolution brain SPECT study performed 26 h after the resolution of the left hemiplegia revealed normalization of the frontal blood flow accompanied by hyperperfusion in the right parietal lobe. An interictal SPECT scan several weeks later showed no asymmetries. Head CT and MRI scans were negative. Neuropsychologic assessment and neurologic examination revealed evidence of a diffuse disorder which predominantly involved the right hemisphere. To our knowledge, there are no previous correlative studies of serial high-resolution brain SPECT with MRI, or of detailed neuropsychologic assessment, in adult patients with such an advanced course of alternating hemiplegia of childhood.

Key words Alternating hemiplegia

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Introduction

Alternating Hemiplegia of Childhood (AHC) is a rare disorder characterized by paroxysmal episodes of hemiplegia or quadriplegia, and other central nervous system manifestations which include dystonic posturing, choreoathetosis, tonic fits, oculomotor abnormalities, and neurocognitive deficits. It is a well-defined entity, first described in 1971 by Verret and Steele [36], but its relationship to migraine and other vascular, neural or metabolic processes has not been clarified. Most cases are sporadic; however, we have previously described the first truly familial occurrence of this syndrome [21]. In this family five individuals in three generations manifested the typical clinical features of AHC. Serial brain SPECT and structural imaging studies, as well as detailed neuropsychological tests performed on an adult member of that family, are reported herein.

Subjects and methods

A 41-year-old man with familial AHC was studied. Neuropsychological assessment was conducted in Spanish during the interictal state, using the Wechsler Adult Intelligence Scale, the Rey-Osterrieth Complex Figure, the Peabody Picture Vocabulary, and Perdue Pegboard tests. Brain SPECT imaging studies were obtained using a dedicated brain SPECT system (ASPECT), after the intravenous injection of 20 mCi (740 MBq) of ^{99m}Tc-HMPAO. The spatial resolution of the system was 6.8 mm (FWHU) for ^{99m}Tc at the center of the field. Transaxial, coronal, and sagittal images were reconstructed using methodology described earlier [11]. Regions of interest were drawn manually over the abnormal-appearing cortex (corresponding to the areas of hyperemia) and the corresponding region on the contralateral hemisphere. Percent differences between the right and left side were calculated for the three SPECT studies. Registration of the three brain SPECT studies with the MRI study using a semi-automatic computed algorithm [12]

was applied. Thereafter, the three brain SPECT studies were resliced according to the MRI slices. For control measurements 22 healthy subjects were studied on the same gamma camera using ^{99m}Tc HMPAO and analyzed semiquantitatively for asymmetry uptake index between regions of the brain ($n = 22$, mean = 1.95 ± 2.06 SD). T1- and T2-weighted MRI of the brain and an EEG were performed.

Case report

The patient was a 41-year-old right-handed male who came to our clinic for evaluation of recurrent episodes of hemiparesis and abnormal movements of the extremities. His condition had reportedly manifested shortly after birth. He had a fifth-grade education, but his performance had been poor due to frequent illness-related absences from school.

The patient had episodes of paralysis of face, arm, and leg on one side or the other, lasting minutes to hours, resolving spontaneously, occurring multiple times a day for several days, often separated by intervals of several weeks' duration. When both sides became involved, it usually occurred in a sequential fashion (rarely with a simultaneous onset) and the patient would become mute. There was no associated loss of consciousness. Spells were preceded or accompanied by sweating, palpitations, difficulty fixing gaze, and occasional difficulty swallowing. After the episodes, he developed a sensation of fullness of his occiput, and if prolonged enough, persistent nausea but no vomiting. The hemiplegia disappeared during sleep, but would sometimes reappear shortly after awakening. Coffee or anxiety, embarrassment, or excitement would precipitate attacks. Decaffeinated coffee did not trigger them. Noisy or crowded surroundings frequently precipitated the attacks. He had received psychiatric assistance for anxiety disorder, and was taking lorazepam for relief of the anxiety which preceded these episodes. Review of systems revealed complaints of a persistent, unusual skin odor and a chronic intermittent epigastric discomfort.

There was also a history of multiple-witnessed episodes of tonic stiffening in the emergency room. These episodes occurred once or twice per month and would involve one or both sides, without loss of consciousness. At the age of 31 years, an episode of "twitching" of both legs was witnessed by a local hospital housestaff member to progress into generalized "major motor seizures" and recovered first on the right side, with the left side remaining stiff for approximately 15 min and with apparent preservation of consciousness. Immediately after, a neurologist noticed him to develop a right flaccid hemiparesis. The patient was transferred to our hospital, where another left hemiplegic spell was accompanied by brief right leg "shaking", followed by mutism and right leg paresis. Briefly after, he had facial grimacing and bilateral hand dystonic movements. An attack of left hypertonicity was once accompanied by mild head tilting to the right. For many years he had been considered to have epilepsy; however, treatment with antiepileptics had been unsuccessful.

Contrary to previous history provided by the patient, it became apparent that he in fact did occasionally experience bilateral severe throbbing headaches which were preceded or accompanied by blurred vision or nausea, and precipitated by stressful events, eating lobster, or prolonged sun exposure. He would ocassionally wake up experiencing a mild headache.

Family history included similar episodes of paralysis in his deceased mother, in a brother, and in two of his three children; none had associated migraine. Head CT scan with and without contrast at the age of 31 years was normal. An EEG at that time showed theta and delta slowing confined to the right temporal region and accentuated by hyperventilation. An EKG showed nonspecific S–T changes; cardiac 2D echo was normal.

Physical examination disclosed a II/IV systolic murmur at the left lower sternal border, minimal left hemi-hypoplasia of the face, and a hyperextendable left knee joint. He had prominent dermographism. He was alert, oriented, and attentive. He had a very limited capacity to write grammatically and read Spanish, his native language. His speech was fluent with occasional circumlocutions. There was minimal dysarthria without aphasia. There was no neglect or right–left confusion. Thought was concrete. He could only perform simple calculations, but was able to manage his money. His ability to draw figures was strikingly poor (Fig. 1). There was a mild facial asymmetry and fragmented pursuit and saccadic eye movements. Motor examination showed mild lingual, buccal, and facial dyskinesias, dystonic posturing and occasional choreoathetotic movements of his left hand and foot, and mildly increased tone in both lower extremities. Strength was normal in all four extremities. Reflexes were normal and symmetric with a left Babinski, found to be present on repeated examinations. Finger to nose, rapid alternating movements, fine finger movements, and heel-to-shin tests were erratic on the left side, probably due to the choreoathetosis. Sensory examination was normal. Romberg sign was absent. Stressed gait testing exacerbated the dystonic posturing of the left hand and foot.

Neuropsychologic examination in the interictal state (3 weeks after resolution of the hemiparesis) revealed a friendly, but somewhat disinhibited and anxious, patient. He had difficulty sustaining attention for tasks, presum-

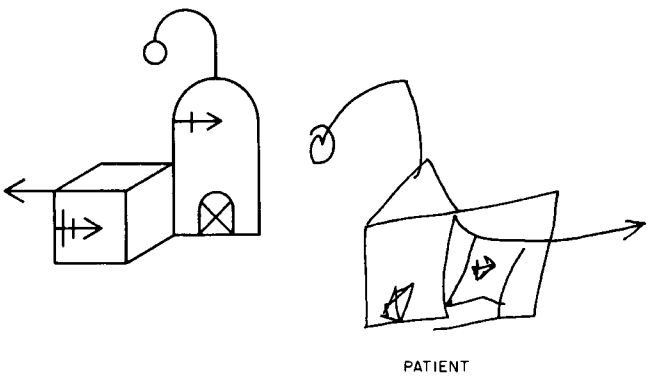

Fig. 1 Interictal difficulty in copying. *Left*: model; *right*: patient's design drawing. Note striking rotation of arrow and 180° shift in the taller figure

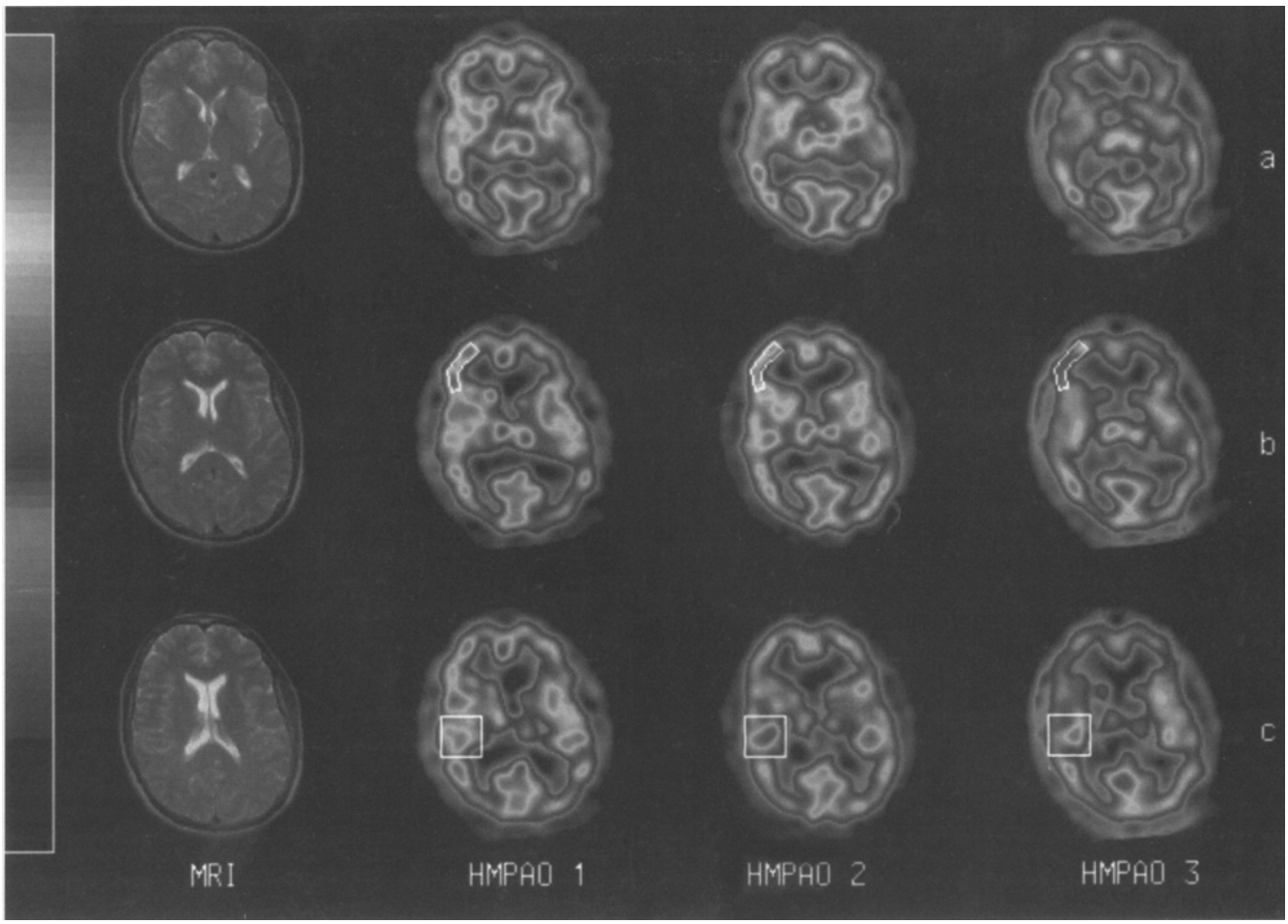

Fig. 2 The images display transaxial slices of our patient's head MRIs and HMPAO-SPECT scans at the level of the basal ganglia, 3 h into (HMPAO 1), approximately 26 h after (HMPAO 2), and several weeks following (HMPAO 3) a left hemiplegic attack. Note the increased right frontal cerebral blood flow (HMPAO 1) which normalizes postictally (HMPAO 2), and the appearance of postictal asymmetry of right parietal tracer uptake (*square*, HMPAO 2). *Bars* at the left display color scales, with zones of decreasing tracer uptake displayed from top of bottom of the image. Minor asymmetries with somewhat lower uptake on one side or the other (e.g., thalamus, temporal lobe, cerebellum, and brainstem) were not seen in other cuts and were considered, by objective visual analysis and by applying side-to-side ratios, to be within the normal variation patterns

ably in relation to his somewhat hyperaroused, anxious state. His performance revealed basic difficulties with organization, problem solving and modulation of behavior. He did not apply trial-and-error strategies consistently to look for solutions. Some evidence of perseverative responding, markedly concrete thinking, and difficulty shifting from one activity to another were noted. Auditory attention span was quite limited: he was only able to repeat three digits forward, and three backward. His conversation was often disorganized and tangential. His language skills were also notable for a slight dysarthria, poor syntax, weak formulation skills, and limited vocabulary and fund of knowledge. Oral reading was notable for poor fluency and diminished attention to prosody and punctuation. Significant visuospatial difficulties were noted with abstract visual processing and perceptual integration tasks. His visual memory was quite limited. He denied ever having visual or auditory hallucinations. The Rey-Osterrieth Complex Figure (ROCF) elicited a markedly distorted, poorly organized copy suggestive of constructional apraxia. Similar findings were noted on the WMS-R visual reproduction designs, with a visual reproduction score of 20 of 41 (4th percentile), and a delayed recall score of 10 of 41 (2nd percentile). On the ROCF immediate recall, he could only remember isolated elements; in contrast, on the ROCF delayed recall, only a rudimentary rectangle was preserved. The overall WAIS-R revealed a prorated full-scale IQ of 56, a verbal IQ of 66 and a performance IQ of 48. The Peabody Picture Vocabulary Test gave a standard score equivalent of 55. The patient's design drawing was at a mental age of 5 years, 6 months. Severe deficits were evident with perceptual motor tasks. Trail making with correction for age and education was significantly impaired. Perdue Pegboard was very impaired on the right; he could not complete this task on the left.

The patient was seen again during an attack of left hemiparesis which lasted 5 h. That day and a few minutes after his left hemiparesis resolved, he had an episode of bilateral tonic stiffening with an opisthotonic-like posturing and mutism lasting less than 1 min. Initially, during the event he had a brief deviation of the eyes to the right,

but within seconds regained ability to fixate and follow with his eyes upon command. No other extraocular movement deficits were evident. Shortly after the episode, he exhibited bilateral hyperreflexia and hypertonia. He subsequently regained normal tone on the right, and over several minutes progressed from diffuse hypertonia to normal tone on the left also. The patient was mute during the episode and for approximately 3 min after its resolution, but was able to follow simple commands and did not appear confused. An EEG performed within half an hour showed no abnormalities. No other similar attacks had occurred within the previous 3 months.

Results

Brain SPECT images 3 h after the onset of left hemiparesis showed increased regional blood flow in the right frontal cerebral cortex (Fig. 2). Twenty-six hours after the resolution of the hemiparesis, a repeat study showed focal hyperperfusion in the right parietal lobe, but normal regional blood flow in the frontal lobes. Comparison between the ^{99m}Tc-HMPAO brain SPECT images showed a medium-sized (2.3 × 1.5 × 1.0 cm) focal area of increased regional blood flow in the right parietal cortex, seen on several slices. The tracer activity in the right parietal region was 6.5% greater than the activity in the corresponding region on the left, compared with a difference of only 2.1% (as in the normal population) in the first study. Several weeks later and while the patient had no hemiparesis, another SPECT scan showed normal brain perfusion (only 3% interparietal difference in tracer activity). Brain MRI showed no structural abnormalities.

Discussion

Since the first description of AHC [36], there have been several attempts to clarify the nature of this entity. Although most cases are sporadic [1], we have previously

Table 1 Functional imaging studies in alternating hemiplegia of childhood. PET positron emission tomography; CBF cerebral blood flow

Reference	SPECT	PET	ICTAL	Interictal	Findings
[29]	+		?	?	Left temporoparietal abnormality
	+		?	?	Decreased CBF left hemisphere (?contralateral)
[37]	+		+	+	Decreased CBF in contralateral hemisphere ictally
					Normal interictal study
[35]		+	+	?	Decreased CBF in contralateral insula, claustrum, and putamen
[31]	+		?	?	Decreased CBF in left frontal and insular areas, and right temporoparietal region
[14]	+		+	+	Increased CBF in contralateral hemisphere ictally
					Normal interictal study
[2]	+		+	+	Increased CBF in contralateral hemisphere (6 patients) ictally
					Normal interictal study (2 patients)
[21]	+		+	+	Normal CBF interictally and 2–3 h into hemiplegic spell
[10]	+		+	+	Decreased CBF in frontal lobe, cerebellum, and brainstem (?contralateral).
					Ictal vs interictal = no change
[32]	+		+		Normal ictal study
	+		?	?	Normal CBF
	+		?	+	Decreased CBF in temporal lobe (?contralateral)
		+	?	?	Normal study
		+	?	?	Normal study
This paper	+		+	+	Increased ictal CBF in contralateral frontal lobe
					Increased postictal CBF in contralateral parietal lobe
					Normal interictal CBF

? = information not available

reported on this patient's family demonstrating an autosomal dominant inheritance with a 46,XY,t (3;9) (p26;q34) translocation [20, 21].

There are only a few investigations of changes of cerebral blood flow during hemiplegia spells [2, 10, 14, 21, 29, 31–32, 35, 37]. The results of these studies are summarized in Table 1. Our study is the only one reporting serial (during, after, and in between attacks in the sample subject) blood flow changes in a patient with alternating hemiplegia. Some studies described decreased cerebral blood flow during the attack [10, 35, 37]. This decrease occurred very early during the attack in one patient, or as late as 36–48 h after its onset in another [37]. Other patients showed no changes in cerebral blood flow when studied at approximately 1–3 h into the attack [21]. The three cases reported by Aminian et al. [2] exhibited hyperperfusion of the contralateral hemisphere 20–60 h into the hemiplegia. Involvement of the ipsi- or contralateral cerebellum by hyperperfusion was also noted in those cases. These patients also had normal SPECT scans in the asymptomatic period. SPECT scan in our patient showed hyperperfusion in the contralateral parieto-occipital region in the posthemiplegic period. The above investigations support a model of dynamic change in cerebral blood flow during and following a hemiplegic spell. It appears that the earliest include hypoperfusion, which may be followed by transient resumption of normal cerebral blood flow and sequential hyperperfusion during the latter part of the attack. Hyperperfusion can persist for up to 26 h after the clinical resolution of the attack as seen in our patient. The posthemiplegia SPECT scan of our patient may have also been influenced by the occurrence of a prominent bilateral tonic posturing episode at the end of that spell.

It has been shown that, in epilepsy, hyperperfusion is demonstrated by SPECT scan only if seizure activity occurred within 5–8 min before tracer injection [27]. This is followed by post and interictal hypoperfusion in the region of the epileptic focus. As suggested by Zupanc et al. [37] and Aminian et al. [2], the above findings are more similar to blood flow changes seen in neurologic migraine [3, 9, 18, 23, 28, 33, 34], in which the initial focal contralateral hypoperfusion is followed by hyperperfusion in the same hemisphere starting 3–8 h after the onset of the symptoms [3]. Persistence of hyperperfusion up to 48 h after resolution of the symptoms, similar to what was observed in our AHC patient, has also been noted in migraine [18]. The occurrence of brainstem signs during hemiplegic spells, the documentation of abnormal brainstem evoked potentials in some patients [31] but not in others [30], and of somatosensory evoked response abnormalities during hemiplegic spells [13] is not inconsistent with migraine-like mechanisms because the posterior circulation is involved in vertebrobasilar migraine.

Despite the above similarities with migraine, several observations suggest that there may be some differences in the mechanisms of generation of the hemiplegic spells in alternating hemiplegia. These observations include the following: (a) the apparently exclusive motor involvement during hemiplegia spells in AHC patients argues that the most important involvement is in the deeper structures rather than in the hemispheres. This is supported by the PET results of Tada et al. [35] who showed contralateral decreased cerebral blood flow to the insula, putamen, and claustrum during hemiplegia of AHC; (b) the apparent lack of visual, sensory and language disturbance in cases of AHC; (c) neurologic signs such as tonic and dystonic posturing either precede or directly follow the hemiplegic spells, frequently occurring in close association with attacks of AHC; (d) unlike patients with migraine, patients with AHC also have other manifestations including developmental delay and extrapyramidal symptoms; (e) the symptoms of anxiety, diaphoresis and palpitations which often herald the onset of the attacks are more typical of AHC than of migraine; and (f) sequential blood flow changes in migraine, although similar, generally show a more consistent pattern of correlation with the clinical picture (i.e., hypoperfusion during the aura and variable hyperperfusion during the headache phase which may persist after resolution of symptoms; see Table 1 [24]). We believe that the above data point to the occurrence of a vascular mechanism, similar to that operating in migraine, which may be accompanied, modified or even triggered by probable neurometabolic derangements, leading to the unique clinical picture of AHC. This view is consistent with the recent evidence suggesting that AHC may be secondary to a mitochondrial abnormality [4].

The episodes of bilateral tonic stiffening observed in our patient could not be shown to correspond clinically to seizures for the following reasons: (a) they had not occurred in relation to his episodes of limb "jerking" (presumably focal seizures); (b) no electrographic abnormalities occurred immediately after the witnessed event; and (c) there had been no response to multiple antiepileptic drug trials. Dystonic and choreoathetotic posturing can occur as ictal phenomena in complex partial seizures of mesial basal temporal lobe onset, prior to head version and contralateral to the ictal discharge, seemingly with distal more than proximal involvement and sparing the head and trunk [15]. Lance [16] reported that seizures arising from the supplementary motor cortex can often present as bilateral tonic muscular contraction with preservation of consciousness, and suggested that tonic seizures could represent a sign of release of basal ganglionic and reticular postural mechanisms from their cortical influence. Our patient did not manifest EEG or clinical manifestations to support seizures of temporal lobe origin; however, because mesial frontal discharges may manifest little or no changes on surface EEG, we cannot completely rule out the possibility that supplementary motor seizures were responsible for some episodes.

Our patient's symptoms best fit AHC rather than any of the previously described familial paroxysmal disorders which present with dyskinesias (dystonia or choreoathetosis) [7, 17, 22, 26], ataxia [5, 8], or with tonic fits [16]. None of these entities manifest as hemiplegic spells (Table 2). Developmental delay and autonomic dysfunction are generally not features of these syndromes, either.

Table 2 Familial paroxysmal neurologic disorders

Some dominant paroxysmal disorders	Prominent symptoms	Trigger	Autonomic symptoms	Treatment/ response	Disturbance	Developmental delay
Paroxysmal cerebellar ataxia [5, 8]	Ataxia	Stress/menses	Sweating, nausea, flushing	Diamox/(+)	Altered pH homeostasis in cerebellum	(–)
Paroxysmal kinesigenic CA [7]	Ataxia, CA, vertigo, dystonia	Stress/motion	(–)	AEDs/(–)	?	(–)
Paroxysmal dystonic CA [17, 22, 26]	Dystonia, CA	Alcohol, fatigue, stress, exercise, excitement, coffee	?	Clonazepam/?	?	(–)
Familial tonic seizures [16]	Tonic fits without loss of consciousness	Alcohol, fatigue, excitement, stress	?	AEDs/?	?	(–)
Familial alternating hemiplegia [21]	Hemiplegia, dystonia, CA, ataxia, tonic fits	Stress, coffee excitement, embarrassment	Sweating, palpitations, difficulty swallowing	Flunarizine(/+) Poor response to AEDs Poor response to Diamox	?	(+)

CA choreoathetosis; (+) has been reported as significant; (–) not reported as significant; ? unknown; AEDs anti-epileptic drugs

Extrapyramidal manifestations are less prominent in AHC. A report of a patient with paroxysmal dystonic choreoathetosis and concomitant familial ataxia [19] raises the question of clinical overlap of some of these syndromes with a possible genetic basis.

It is interesting to note that the translocation in our patient and in his other affected family members is located on 9q32–q34 close to where the locus for idiopathic torsion dystonia (ITD) [25], and the locus for the enzyme argininosuccinate synthetase (ASS) are [6]. This finding, however, may not be significant because it is clear that our patient has neither ITD nor ASS deficiency. Thus, although the association of the translocation itself with AHC may be indicative of the location of the AHC gene, it still may represent a coincidental finding [20–21].

A poor long-term neurologic and mental prognosis for this disorder is part of the current diagnostic criteria for AHC [36]. Our investigation of this adult patient with the familial form of AHC supported that criterion and revealed evidence of diffuse as well as unilateral hemispheric involvement, as evidenced by the following: (a) right temporal slowing on the interictal EEG, and (b) evidence of diffuse bilateral as well as focal right hemisphere dysfunction by neuropsychologic assessment. These findings had no structural correlation by CT or MRI, which suggests that the pathogenesis is not related to multiple or recurrent regional infarctions. Our findings are consistent with an underlying, possibly fluctuating metabolic dysfunction with superimposed vascular spasms, with the latter presenting as a dynamic process. The interaction of the two factors may lead to regional vulnerabilities and cumulative effects resulting in a chronic brain syndrome with some focal manifestations. More studies of adult patients with this syndrome will be needed to further document the profile we found. Furthermore, the potential heterogeneity of the mechanisms underlying the sporadic and the familial forms of this syndrome also need to be closely examined.

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