Crossed Cerebellar Atrophy in Patients With Precocious Destructive Brain Insults

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Objective: To analyze the frequency and pathogenetic factors of crossed cerebellar atrophy (CCA) in adult patients with epilepsy secondary to destructive brain insults of early development.

Methods: We studied 51 adult patients with epilepsy and precocious destructive lesions. Patients were divided into 3 groups according to the topographic distribution of their lesions on magnetic resonance imaging: group A, hemispheric (n=9); group B, main arterial territory (n=25); and group C, arterial border zone (n=17). We evaluated the presence of CCA visually and with cerebellar volumetric measurement, correlating it with the clinical data. Other features shown on magnetic resonance imaging, such as the thalamus, brainstem, and middle cerebellar peduncle, were also carefully analyzed.

Results: Seven patients (13%) had CCA that was associated with the extent of the supratentorial lesion (6 from group A, 1 from group B, and none from group C; \( P < .001 \)). Status epilepticus was present in 6 patients from group A and in none from the other groups. There was an association between the antecedent of status epilepticus and CCA (\( P < .001 \)). All patients had atrophy of the cerebral peduncle ipsilateral to the supratentorial lesion and 4 had contralateral atrophy of the middle cerebellar peduncle. The duration of epilepsy was not associated with the presence of CCA (\( P = .20 \)).

Conclusions: Our data suggest that in patients with epilepsy and destructive insults early in life, the extent of the supratentorial lesion as well as the antecedent of status epilepticus play a major role in the pathogenesis of CCA. Recurrent seizures do not seem to be relevant to the development of CCA.

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A TROPHY of the cerebellum contralateral to a hemispheric supratentorial lesion, or crossed cerebellar atrophy (CCA), has been recognized by neuropathologists for more than 100 years but the understanding of its pathogenesis is still incomplete.1-7

In 1980, Baron et al8 described contralateral cerebellar hypometabolism (CCH) in positron emission tomographic (PET) images of adult patients with supratentorial infarcts, calling it crossed cerebellar diaschisis. Diaschisis is also an old concept, classically defined as a transient impairment of functional activity in an area remote from the site of a primary lesion.9,10 However, the interpretation of CCH as a diaschisis is challenged since there are several instances in which the CCH lacks reversibility.11,12 Thus, a reversible diaschisis and an irreversible atrophy can hypothetically constitute the extremes of a continuum of the same biological process. Damage to the corticopontocerebellar pathway is the most accepted pathogenic mechanism in the development of CCH or CCA.13-15 There is also a robust body of evidence on the destructive effects of prolonged seizures in vulnerable regions of the brain and on the damage caused by partial status epilepticus (SE) to the contralateral cerebellum.16-20

The role of the extension of the cerebral lesion in CCH is not fully understood since it has been associated with the degree of CCH in some studies11,21 but not in others.22,23 Furthermore, the role of recurrent seizures in the development of CCH or CCA is not yet clear.24 To further investigate the pathogenesis of CCA, we reviewed the results of magnetic resonance imaging (MRI) in a series of patients with epilepsy and different types of destructive lesions of early development to assess whether there is any particular MRI or clinical feature related to CCA.
METHODS

We evaluated the MRI results of 51 consecutive adult patients with the diagnosis of epilepsy secondary to a destructive brain lesion of early development, who were seen at our institution from March 1999 to April 2001 (median age, 31.8 years; range, 15-55 years). Detailed histories of prenatal, neonatal, and early childhood events were systematically reviewed in the medical records, and direct interviews with the patients and their relatives were conducted. All patients had disease onset before the age of 5 years; we excluded all patients with evidence of adult-onset disease. Informed consent was obtained from all subjects. This study was approved by the ethics committee of the faculty of medical sciences of University of Campinas (Campinas, Brazil).

Magnetic resonance imaging was performed by a 2.0 T scanner (Elscint Prestige, Haifa, Israel). Our epilepsy protocol consists of: (1) sagittal T1 spin-echo, 6 mm thick (repetition time [TR], 430; echo time [TE], 12) for optimal orientation of the subsequent images; (2) coronal T1 inversion recovery, 3 mm thick (tip angle, 200°); TR, 2700; TE, 14; TI, 840; matrix, 130 × 256; field of view [FOV], 16 × 16 cm); (3) coronal T2-weighted fast spin-echo, 3 to 4 mm thick (tip angle, 120°; TR, 4800; TE, 129; matrix, 252 × 320; FOV, 18 × 18 cm); (4) axial images parallel to the long axis of the hippocampus; T1 gradient echo, 3 mm thick (tip angle, 70°; TR, 200; TE, 5; matrix, 180 × 232; FOV, 22 × 22 cm); (5) axial T2 fast spin-echo, 4 mm thick (tip angle, 120°; TR, 6800; TE, 129; matrix, 252 × 328; FOV, 21 × 23 cm); and (6) volumetric (3-dimensional) T1 gradient echo, acquired in the sagittal plane for multiplanar reconstruction, 1 to 1.5 mm thick (tip angle, 35°; TR, 22; TE, 9; matrix, 236 × 220; FOV, 23 × 25 cm).

Visual analysis of MRI results was systematically performed by one of us (S.L.M.S.), blinded to the clinical data, in a workstation (Silicon Graphics O2; Silicon Graphics Computer Systems, Mountain View, Calif) using Omnipro software (Elscint Prestige). Curvilinear reconstruction of 3-dimensional MRI volumetric images was performed in all patients by a Power Macintosh (Apple Computer Inc, Cupertino, Calif) using the BrainSight software (Rogue Research, Montreal, Quebec). This approach was very helpful for clear visualization of the extent of cortical involvement and allowed us to classify the patients into 3 different groups according to the topographical distribution of the lesion: group A, hemispheric lesions, defined as a diffuse atrophy of an entire hemisphere without loss of tissue continuity (n = 9); group B, lesions limited to a main arterial territory, often constituting a cavity (n = 25); and group C, lesions on the border zones between the main cerebral arterial territories (n = 17)3,4 (Figure 1). Special attention was also focussed on the morphology of the brainstem, thalamus, cerebellum, and middle cerebellar peduncle.

In addition, we performed volumetric measurements of the cerebellums of all patients using a semiautomatic software program (NIH-Image; National Institute of Health, Bethesda, Md). The cerebellum was manually outlined on sagittal slices. To check right-left asymmetry, the measurements were distributed into right and left cerebellum according to the position of the cerebral aqueduct. When only 1 slice showed the cerebral aqueduct, half of its measurement was computed to the right cerebellum and the other half to the left. More commonly, 2 slices showed the cerebral aqueduct, and in these cases, each slice was computed to each hemispherium. The extracerebellar portion of the middle cerebellar peduncle was not included and this limit was assumed as the angle formed between the cerebellar hemisphere and the middle cerebellar peduncle.

The cerebellums of 12 healthy volunteers were measured and constituted a control group. An asymmetry index (AI) was calculated for each subject by subtracting the right hemispherium volume from the left and dividing by the mean of the right and left. Values outside 2 SDs (95% confidence interval) from the AI mean of the control group were considered abnormal. Cerebellar volume was normalized to the total brain volume to check for bilateral atrophy.

We used the Pearson χ² test and Fisher exact test for comparisons between proportions. An analysis of variance and the Tukey post hoc pairwise comparison were applied for comparison on continuous variables among the 3 groups. We used the Pearson correlation test to assess correlation between duration of epilepsy and cerebellar volumes. The significance level was .05.

RESULTS

Crossed cerebellar atrophy was visually identified in 6 patients. The volumetric studies confirmed the CCA in these 6 patients and in a seventh patient whose visual analysis did not definitively point to CCA. A visual diagnosis of bilateral cerebellar atrophy was made in 9 patients, all of whom had long-term exposure to phenytoin. These patients showed thinner folia but had preservation of the cerebellar contour dimension so that while results of their volumetric studies tended to be abnormal, they did not reach significance. None of the patients with cerebellar atrophy had clinical cerebellar signs.

Six of the 7 patients with CCA belonged to group A (hemispheric) and 1 to group B (arterial territory) (Figure 2). All 6 patients from group A had the antecedent of SE in the first 5 years of life, developing a permanent hemiparesis just after the SE. In 4 patients, SE associated with a febrile illness was the first manifestation of their disease. Two patients had SE after experiencing uncomplicated seizures, 1 of them since the neonatal period. The single patient from group B did not experience any episodes of SE and had the first seizure at age 27 years. This patient had a right hemiparesis observed in the first year of life without any potentially associated morbid event and had a large cystic infarct in the territory of the left middle cerebral arterial territory, pointing to a prenatal insult. Patients with CCA exhibited the SE antecedent more commonly (6/7) than those without CCA (2/44) (χ² = 22.49; P < .001). The SE antecedent was by far more common in patients in group A (8/9) than in the other groups (group B, 1/25; group C, 1/17) (χ² = 30.39; P < .001).

The duration of epilepsy and seizure frequency were similar between the groups and were not different in patients with CCA (P > .05). Recurrent generalized convulsions throughout the course of epilepsy were more fre-
quent among patients in group B (7/25) than groups A (0/9) and C (1/17) but the difference was not statistically significant ($P > .05$). The frequency of generalized convulsions was also not different between patients with CCA and those without ($P > .05$). Three patients from group A (33.3%), 6 patients from group B (24%), and none from group C exhibited hemiconvulsions as a habitual seizure type ($P > .05$). Hemiconvulsions were equally frequent among patients with CCA and those without CCA ($P > .05$).

Ictal semiology exclusively of the temporal lobe was observed in 17 patients (33%) and it was more common among patients in group C ($\chi^2 = 11.41; P = .003$). Analysis of variance demonstrated that the AI was different among the groups ($F_{2,48} = 7.63; P = .001$) and post hoc comparison showed that group A (mean, 3.83) was significantly different from groups B (0.99) and C (0.82). Furthermore, no correlation was found between duration of epilepsy and AI ($R^2 = 1.11; P = .3$).

Four of the 7 patients with CCA exhibited atrophy of the middle cerebellar peduncle contralateral to the supratentorial lesion. The other 3 patients with CCA without atrophy of the cerebellar peduncle all exhibited the antecedent of SE. In contrast, patients without CCA did not exhibit atrophy of the middle cerebellar peduncle.

Atrophy of the ipsilateral cerebral peduncle was more commonly observed in patients from groups A (8/9) and B (18/25) than from group C (4/13) ($\chi^2 = 13.89; P = .001$). All patients with CCA had ipsilateral cerebral peduncle atrophy and 2 of them also exhibited atrophy of the ipsilateral pons (Figure 3). Ipsilateral thalamus involvement was more frequent in patients from groups A and B (5/9 and 17/25, respectively) than in group C (2/15) ($\chi^2 = 13.16; P = .001$). There was atrophy of the ipsilateral thalamus in all patients with CCA except one. Both thalamus and brainstem involvement were associated with the presence of CCA (Fisher exact test, $P < .005$).

In their classic article, Verhaart and Van Wieringen-Rauws observed that CCA tends to be associated with long-standing, extensive unilateral lesions of the cerebral hemisphere, usually originating in infancy or early childhood. Thirty years later, Baron et al described CCH observed on PET scans of adult patients with supratentorial infarcts, suggesting that it represents the "early metabolic correlate of the phenomenon of CCA." Since then, it has been well accepted that CCH and CCA constitute a spectrum of the same biological process but the factors that determine a reversible and functional phenomenon (CCH) to become an irreversible structural change (CCA) are still not fully understood.

Tien and Ashdown were the first to report the possible connections between CCH and CCA, analyzing the MRIs of patients with CCH observed on PET scan images. They found that 8 of 26 patients with CCH also had CCA. All 8 patients had long-standing unilateral hemispheric atrophy with intractable focal seizures. Conversely, most patients without CCA had cerebral tumors larger than 3 cm, and only 40% had seizures. Those patients were older and had shorter duration of symptoms than the patients with CCA. This study suggests that the differentiation of CCH from CCA depends on the nature and extension of the lesion and the duration of symp-
Urich15 described the necropsy findings of a patient who died 2 days after a lateralized SE and compared them with findings from 3 necropsies of patients who had exhibited the antecedent of SE months or years before death. The pathologic findings included laminar cortical necrosis in the left hemisphere associated with a marked loss of Purkinje cells in the right hemicerebellum. The presence of eosinophilic changes on many of the remaining Purkinje cells of the affected hemicerebellum pointed to recent damage. In addition, MR diffusion-weighted images (2 days before death) showed abnormal diffusion throughout the cortex of the left hemisphere and right hemicerebellum.

Other authors have suggested that repetitive seizures could be a main pathogenetic factor in CCA,5,8,24 Our study does not support this concept since the duration of epilepsy and seizure frequency was similar between the groups and it was not different among the patients with CCA. In addition, the pattern of seizure semiology did not seem to have an effect on CCA in our series. Neither hemiconvulsions nor generalized convulsions recurring long after the onset of epilepsy were different among the groups or between patients with CCA and those without. Patients with arterial border zone lesions more commonly exhibited monomorphic seizure semiology with a temporal lobe–like pattern (probably reflecting their less extensive lesions), and we cannot discard the possibility that this might be associated with the absence of CCA in this group of patients. However, it seems unlikely that seizure semiology had a greater influence on CCA compared with the extension and bilaterality of the lesion in these patients. Given the few patients with CCA, it is likely that the power of this study is insufficient to conclude that there is a definite negative relationship between habitual seizures and CCA.

There is evidence that transneuronal degeneration has a decisive role in the pathogenesis of CCA. Necropsy studies of patients with CCA commonly show atrophy of the middle cerebellar peduncle contralateral to the supratentorial lesion and in the nuclei of the ipsilateral pons.14,15 A more recent work, using PET studies of patients with supratentorial tumors, showed a significant reduction in glucose metabolism in the ipsilateral pons parallel to CCH.13 Patients with long-standing su-
pratentorial damage but no history of seizures can occasionally develop CCA.27,28 Moreover, there is a report that describes a patient who developed CCA after a hemispherectomy for seizure control.29

Cerebral peduncle atrophy ipsilateral to the supratentorial lesion was significantly associated with CCA in our study. This can be interpreted as a sign of wallerian degeneration but can also represent the primary lesion. Conversely, the contralateral middle cerebellar peduncle atrophy observed in 4 of the patients with CCA should be considered as a sign of transneuronal degeneration associated with damage to the corticopontine-cerebellar pathway.15 One of these patients did not have the SE antecedent; the transneuronal degeneration seemed to be the main mechanism of CCA in this case. In contrast, there were 3 patients without atrophy of the middle cerebellar peduncle but who had a history of SE. In these cases, SE may have been the cause of CCA, even without late transneuronal degeneration.

Another possible factor involved in the pathogenesis of CCA is the damage to the cerebellorubrothalamic tract leading to a retrograde CCA.30 Atrophy of the thalamus was significantly associated with the presence of CCA in our series. However, it may have been just the reflex of the extension of the lesion since it was also more frequent among patients in groups A and B, who had larger lesions. Therefore, it is not possible to determine the relative importance of retrograde CCA in these patients.

In conclusion, our study suggests that in patients with long-standing destructive brain lesions and epilepsy, SE as well as the extent of the supratentorial primary lesion play major roles in the development of CCA. Our data also suggest that recurrent seizures are not relevant to the development of CCA.

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