SUPRATENTORIAL FUNCTIONAL DISTURBANCES IN TWO CHILDREN WITH CEREBELLAR CORTICAL DYSPLASIA

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SUMMARY
When evaluating children with mental retardation, subtle cerebral and cerebellar morphologic anomalies are often noted at Magnetic Resonance Imaging (MRI). Some, such as cerebellar cortical dysplasia (CCD), have been considered as subtle markers of cerebral dysgenesis. Their functional significance and their effect on brain function, remain unknown. To study supratentorial functional disturbances related to CCD we performed Positron-Emission-Tomography (PET) studies in two children with isolated CCD, in order to investigate the degree of involvement of supratentorial structures. One had developmental delay, motor disturbances and ataxia, and the other one only had mental retardation. PET studies revealed hypoperfusion and hypometabolism within the vermis, thalamus and the right striatum in one case, and hypometabolism in the basal ganglia and cerebellar deep grey nuclei in the other case. Our results could lead to a hypothesis explaining motor disturbances as well as cognitive impairment, and could suggest a pathological functional significance of CCD. Nevertheless, the relationship between these findings and mental retardation needs further investigation.

Key words: MR Imaging, PET, cortical dysplasia, cerebellum.

RÉSUMÉ
Anomalies fonctionnelles supratentorielles chez deux enfants porteurs d’une dysplasie corticale cérébelleuse
Lors du bilan de retard mental chez certains enfants, l’imagerie par résonance magnétique (IRM) a démontré quelques anomalies morphologiques cérébrales et cérébelleuses. Certaines d’entre elles, telle que la dysplasie cérébelleuse corticale (DCC), ont été considérées comme de discrets marqueurs de dysgénésie cérébrale. Leur signification fonctionnelle et leur répercussion sur le fonctionnement cérébral global restent mal connues. Pour étudier les perturbations fonctionnelles en rapport avec la DCC, nous avons réalisé des études du métabolisme et de la perfusion cérébrale par Tomographie par émission de positons (TEP) chez deux enfants porteurs d’une DCC isolée, dans le but d’évaluer le retentissement supratentoriel fonctionnel de l’anomalie morphologique cérébelleuse. L’un avait un retard mental, des troubles moteurs et une ataxie, et l’autre, un retard mental avec quelques discrets troubles moteurs. Les études menées au TEP ont révélé une hyperperfusion et un hypometabolisme au sein du vermis, thalamus et du striatum dans le premier cas et un hypometabolisme au sein des noyaux de la base dans le second cas. Nos résultats pourraient suggérer une hypothèse expliquant les troubles moteurs et cognitifs dans de tels cas, d’une part, et d’autre part nous font évoquer une signification fonctionnelle pathologique de la DCC. Toutefois, la compréhension du rapport entre cette anomalie morphologique cérébelleuse et les altérations fonctionnelles supratentorielles nécessite qu’un plus grand nombre de cas soient investigués.

Mots-clés : IRM, TEP, dysplasie corticale, cervelet.

INTRODUCTION
When evaluating children with mental retardation (MR), subtle findings are often noted at MRI such as mega cisterna magna, hypoplasia of the corpus callosum, wide cavum septum pellucidum, white matter alterations, heterotopia, cerebellar or vermian hypoplasia and cerebellar cortical dysplasia (CCD) [4-6, 10, 12, 19-23]. These anomalies have been considered as subtle markers of cerebral dysgenesis but their effect on brain function, the nature of the underlying brain dysfunction and their role in the pathogenesis of mental retardation remain unknown. The involvement of the cerebellum in cognitive functions has been studied but is still not well understood [14, 16, 24]. Functional brain evaluation could be useful to detect some anomalies and therefore give more information to understand the pathological process in neurological and neuropsychological abnormalities found in CCD. In this study, we performed PET studies in developmentally delayed children with isolated CCD diagnosed by MRI. We investigated the involvement of structures outside the cerebellum and how remote loss to those structures due to cerebellar dysplasia may affect cognitive functions. To our knowledge, no previous study reported PET findings in patients with MR diagnosis of CCD. We explored the possibility that CCD may be associated with altered brain functions.
CASE 1

Clinical data

This patient was the firstborn child of a non consanguineous and healthy couple. The clinical background during pregnancy revealed maternal bleeding during the first trimester and detachment of the placenta until 3 months. A menace of prematurely delivereance occurred at 7 months. In June 1998, delivery was performed by caesarian section because of breech position and narrow pelvis. The Apgar scores were 10/10 and 10/10 at 1 and 10 minutes respectively. The birth weight was 2260 g and the head circumference at birth was 33 cm. Mild axial hypotonia with head and trunk ataxia and proximal brachial motor deficit associated with developmental delay were diagnosed at 6 months of age. Physical examination revealed minor facial deformities (bilateral epicanthus, enlarged forehead and small mouth with thin lips) and talus valgus feet. Further clinical, metabolic and genetic investigations, including infection, metabolic tests and high resolution karyotype were carried-out without positive results. The child progressed in a slow evolution characterized by mild mental retardation, motor disturbance and cerebellar syndrome. In June 2000, an MRI was done to evaluate for cerebral malformations and a Brain PET study to detect any functional abnormality.

MRI findings

The images were acquired with a 1.5 T unit (Siemens, Erlangen, Germany), including three-dimensional high resolution T2 weighted images (5000/120/2: TR/TE/ex), and Inversion Recovery (11520/400/60/2: TR/TI/TE/ex), in the sagittal and coronal orthogonal planes. MRI showed inferior vermian hypoplasia, abnormal delineation of vermian primary fissures (figure 1a) and atypical aspect of cerebellar hemispheric fissures suggesting CCD (figure 1b). No supratentorial morphologic anomalies were seen.

PET study

The purpose and methods of the PET study were explained to the parents of the child and written informed consent was obtained. Relative cerebral blood flow (rCBF) was determined from the distribution of radioactivity measured with high-resolution PET cameras after bolus intravenous injections of 7 mCi of $^{15}$O$\text{H}_2\text{O}$ fifteen seconds before each scan. PET studies were obtained on a Siemens ECAT Exact HR+962 camera (Knoxville, Tenn.). Data were collected over a period of 80 seconds and reconstructed into 63 slices, with a resulting resolution of 5 mm full width at half maximum. Brain metabolism was investigated after an intravenous bolus of 2 mCi (74 MBq) of FDG was injected before PET acquisition in 3D mode. PET study was conducted at rest during sleep induced by sedation with 4 mg/kg of pentobarbital sodium. FDG-PET data analyses were performed using a voxel-based method, Statistical Parametric Mapping (SPM99, Wellcome Department of Cognitive Neurology, London, UK). Our results were compared to a selected group of 10 children with MR without cerebellar or brain malformations (8 males and 2 females). PET study revealed significant ($p<0.001$) vermian, bi-thalamic and right striatal hypoperfusion and hypometabolism (figure 2).

CASE 2

Clinical data

The second child, a female, was born prematurely at 36 weeks of gestation. The parents were...
Fig. 2. – (a-c) FDG PET scan shows that regions with significant hypometabolism are restricted to the ventral right thalamus, and the right striatum and caudate nucleus (white arrows); (d-e) and (f-g): perfusion PET studies show regions with significant hypoperfusion, within the vermis and thalamus (coregistration with axial T1-weighted anatomical images).
non consanguineous and healthy. There was no threatening event during pregnancy and the delivery was normal. At birth, the Apgar score was 10/10 at 1 and 10 minutes respectively. The birth weight was 2170 g, and the head circumference was 31 cm. The examination at birth found dysmaturity and left fourth toe hypoplasia. The presented for the first time with seizures at age 7. Neurological investigations were consistent with a diagnosis of epilepsy with partial seizures and the girl underwent antiepileptic treatment. Four years later, because of seizure recurrence, she presented one more time at the hospital to adjust the treatment. Then, the neurologist and psychologist, after examination, found mild mental retardation with specific disturbances of reading, writing and speech. Fine motor coordination disorders, without ataxia, as well as spatial organization and orientation difficulties were also found. These clinical features and the search of epilepsy etiology led to brain MRI and PET study.

MRI findings

The examination was performed on a 1.5 T Philips Gyroscan Intera system (Best, The Netherlands) including thin slices and high resolution three-dimensional T1 weighted images (30/4.6/30°: TR/TE/ex), T2 weighted (3000/100/90°: TR/TE/ex) and Inversion Recovery (1645/300/30/90°: TR/T1/TE/ex) in the axial and coronal planes. The axial modular inversion recovery image showed an abnormal orientation of cerebellar fissures on the left inferior hemisphere, corresponding to focal cortical dysplasia, also seen on coronal T2 image (figure 3). This anomaly also affected the right hemisphere but was more subtle. The vermis was normal and no supratentorial morphological anomaly was detected.

PET study

PET scan was obtained using a CTI-Siemens ECAT 962 (HR+) tomograph. The patient was awake at the time of FDG injection and fasted for 4 hours. An intravenous bolus of 2 mCi (74 MBq) of FDG was injected before PET acquisition in 3D mode. The patient was not sedated for PET data acquisition. FDG-PET data analyses were performed using a voxel-based method, Statistical Parametric Mapping (SPM99, Wellcome Department of Cognitive Neurology, London, UK). Patient’s cerebral glucose metabolism was compared with that of 26 right handed healthy controls (10 males and 16 females, aged 18 to 42 years, mean age=28). This study revealed the presence of a significant (p<0.05) decrease of glucose metabolism in both basal ganglia (figure 4a), more obvious in the lentiform nuclei as shown on figure 5. In the posterior fossa, there was also hypometabolism at the level of the deep grey cerebellar nuclei (figure 4b and 4c). Perfusion studies were not obtained.

DISCUSSION

Our studies show areas of brain dysfunction associated with morphological cerebellar anomalies in two children with CCD. These results may suggest a profound effect of discrete cerebellar lesions on brain function. Accordingly to Shaefer et al. [22], our results confirm the increased ability of neuroimaging techniques to define brain anatomy and to detect many findings representing markers of brain dysgenesis in patients with impaired cognitive functions. In addition to brain perfusion and metabolic impairments, our results showed, in case 1, hypoperfusion within the vermis that was well correlated with the area of CCD diagnosed by MRI, and in case on the same side as the cortical dysplasia.
Up to now, the majority of functional imaging studies have been done in infants without structural cerebellar anomalies at MRI. Based on observations in cerebral-cerebellar connections, a body of neurological and neurophysiological evidence and functional imaging techniques suggest that the cerebellum is incorporated into the neural circuitry that has diverse role in brain function: non motor, sensory, vegetative, affective and cognitive [14, 16, 24]. Recent anatomical and physiological studies have shown that the cerebellum, the thalamus and the striatum are connected in organized circuits or “loops” that are connected with diverse cerebral areas. The similar properties of neurons within the components of each circuit suggest that individual loops could be involved in distinct behavioral functions [14, 15]. In our study, functional abnormalities found in infra- and supratentorial regions support the existence of cerebellar-thalamic-striatal circuitry. The association between hypometabolism and cortical dysplasia is not clearly understood, but one the hypotheses is the impairment of neuronal connectivity.

Damage to the cerebellum and basal ganglia is known to produce alterations in motor function and are thought to be due to disruption of cerebellar and basal ganglia outputs to cortical areas involved in the control of movement. Ataxia (in case 1) and motor disturbances (in both cases) have been diagnosed; nevertheless PET studies did not show cortical anomalies. On the other hand, a number of observations published in the literature in the last decades, have described connections between the cerebellum, basal ganglia and other cortical areas involved in high-order functions suggesting a role for the cerebellum and basal ganglia in cognitive functions [1, 9, 15]. In this setting, Houk et al. [9] suggested that the properties of functional organization in cerebellar and basal ganglia circuitry resembles the properties of the motor function circuit integrated by the cerebellum, basal ganglia and the motor cortex. Moreover, many nodes, prefrontal, thalamic and cerebellar are probably linked on cognitive network by virtue of their connectivity. Parsons et al. [16] suggested that cognitive operations may involve the prefrontal cortex acting on ideas and concepts that are encoded in the parietal and temporal cortex, under regulatory influences from the limbic system, the basal ganglia and the cerebellum. In some patients with cognitive dysfunction, neuropathological studies revealed decreased frontal size with thin cortex and substantial thalamic dorsal nucleus cell loss without signs of gliosis, suggesting a developmental rather than degenerative underlying process. Neurofunctional imaging in the same patients showed a hypofrontality, defined as a failure of prefrontal cortex to increase its flow during an experimental task [1]. Our patients had motor disturbances associated with developmental delay and MR.

In some patients, levels of brain perfusion were closely related to the severity of MR. Kao et al. [10] in a SPECT study reported high levels of hypoperfusion in cases with severe MR as compared with mild mental retarded patients. In patients with MR of diverse etiology and in patients with abnormal cognitive function, functional studies using SPECT or PET scans detected consistent extensive perfusion impairments. In autistic children Ryu et al. using SPECT detected hypoperfusion in the cerebellum, thalamus and parietal cortex [18], whereas in PET studies, the hypoperfusion was detected in the temporal lobes [26]. In Down syndrome, hypoperfusion was present in parieto-occipital, temporoparietal and frontal lobes in children and in tempo-parietal regions in adults [8]. In perinatal asphyxia, perfusion impairments involved the cerebral cortex and the cerebellum, thalamus and basal ganglia.
Finally, in children with fetal alcohol syndrome, mild hypoperfusion of the left parieto-occipital region and a lack of normal left-right dominance in the frontal area had been detected [17]. To our knowledge we report the first PET perfusion studies in a patient (case 1) with CCD. The cortical and subcortical hypoperfusion and regional hypometabolism seen in MR of diverse etiology and data published about cognitive defects found in patients with cerebellar lesions and probably due to damage of structures outside the cerebellum through its supratentorial connections, lead us to wonder whether in our patients, CCD may have a role in the expression of motor disturbances and mental retardation.

In our study, the lack of structural anomalies in supratentorial cortical areas could be explained by the fact that the connectivity of the neuronal cognitive circuitry could be disturbed at cellular (neuronal migration, cellular alignment, dendrite, spine formation or synapse and apoptosis) [1] or at molecular levels that cannot be identified by morphologic imaging studies [13]. This statement has been recently confirmed at magnetic resonance spectroscopy (MRS) in MR in which decreased levels of NAA/Cr ratio and increased levels of Cho/Cr ratio suggested synaptic diminution and/or disruption or hypomyelination [7]. Thus, a recent consensus on neuroimaging in developmental delay recommends including MRS [2, 3].
It is becoming clear that cerebellum plays an important role in many diverse functional systems of the human brain. Our findings, could explain motor disturbances that have been diagnosed in these children and may suggest a pathological significance of CCD. Functional imaging investigations are not yet recommended as a systematic part of the evaluation of children with global developmental delay [2, 3]. Nevertheless, further longitudinal studies are needed to determine whether these findings can be markers of developmental delay. PET and MRS experiments and neuro-psychological evaluation should be aimed directly at identifying the functional role of the cerebellum in order to propose a probable role of cerebellar cortical malformations in the expression of MR.

CONCLUSION

These two cases emphasize the increasing interest on neuroimaging techniques as MRI and PET, in understanding the relationship between CCD and MR. The functional disturbances observed on PET studies in supratentorial structures lead to the hypothesis that CCD could induce an impairment of cognitive functions by interfering in the cerebellar-thalamic-striatal circuitry. Further functional investigations including spectroscopic investigations, in a larger number of patients, will certainly contribute to our better understanding.

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