CASE REPORT

Degeneration of the Arnold’s prefrontopontocerebellar tract in a case of locked-in syndrome over a 23-year period

Dégénérescence du faisceau préfontopontocérébelleux d’Arnold dans un cas de locked-in syndrome sur une période de 23 ans

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Summary
A 52-year-old woman has been under observation for a complete locked-in syndrome of vascular origin, since 1984. Her cognitive functions today are still normal. When first diagnosed, a CT-scan was made and 23 years later performed, a cerebral MRI was performed. A focal, bilateral and symmetric atrophy of the dorsomedial prefrontal gyri was clearly shown, contrasting with the non-atrophy of the precentral gyri (motor area), others prefrontal areas, frontopolar gyri and temporal cortices. Degeneration of the corticopontine projection, the first step in the corticopontocerebellar circuit, could explain this selective atrophy. This unique observation leads to the precise in vivo anatomical location of the Arnold tract.

Introduction

The term ‘‘locked-in syndrome’’ (LIS) describes patients who are completely paralyzed, except usually for eye or eyelid movements, but have a normal mental state\cite{[1]}. Those patients most often have suffered a pontine stroke.
Arnold tract degeneration or haemorrhage [2]. Survival range from 2 to 18 years in a population of 29 locked-in syndrome patients in one cohort analysis [3] and up to 27 years in one case [4]. Cognitive abilities can be preserved even after 12 years [5,6]. So far, however, no information has been given about the corticospinal tracts, primary motor and premotor cortices, and prefrontal areas following a long-standing de-efferentation. The area of the prefrontal cerebral cortex involved in the cortico-pontocerebellar system remains unclear.

We give here a precise and thorough anatomical study of those structures and that system based on the MRI exploration of a 23-year locked-in syndrome case.

**Patient and methods**

The patient is a 55-year-old woman who left school at the age of 14 without achieving the elementary school certificate. She worked as a hairdresser. In December 1984, she suddenly became comatose following a chiropractic cervical manipulation for chronic posterior headaches. When she was admitted, no spontaneous movement of the four limbs was noted. A CT-scan carried out 2 days later showed a slightly ventral hypodensity located in the brainstem without damage in either the cerebral hemisphere or the cerebellum (Fig. 1). Vertebral angiography showed a basilar artery thrombosis. She regained consciousness 2 weeks later and was transferred to a neurological rehabilitation unit 1 month later. When admitted her, a neurological examination revealed an upper motor neuron quadriplegia. Horizontal, vertical eye movements and eye opening were possible but limited. No voluntary facial and mouth movements were noted. There was a complete oropharyngeal paralysis. She underwent a tracheostomy. Superficial and deep sensations were intact.

At the time of examination, 23 years later (2007), the clinical status remained unchanged, with a persistent quadriplegia and a complete oropharyngeal paralysis. Visual acuity and audition were preserved. The patient lived with a tracheostomia and a gastrostomia. The patient was cooperative. She has no apnea syndrome. The patient was well oriented in time and space. She had no mood disorder, nor psychotropic treatment. Her behaviour was adapted to life in the unit with an efficient communication code. Communication was made possible through questions requiring yes/no answers: she could answer by moving his eyes upward for “no” and by closing eyes for “yes”. Her answers were always appropriate. Moreover, during that long period, the patient learnt to use a computer interface permitting the use of a keyboard and an access to the intranet and mail.

A neuropsychological assessment of her executive functions was carried out with the Wisconsin Card Sorting Test [7]. The patient answered questions using the morse alphabet. Her responses were displayed on the computer screen. The patient performed 72 trials (normal values: $87.42 \pm 19$) with 61 good answers (normal values: $67.85 \pm 19$), 11 wrong answers (normal values: $19.57 \pm 17$). The percentage of wrong answers was 15 (normal values: $20 \pm 12.78\%$). The number of perseverations was six (normal values: $10.8 \pm 12.8$) with a percentage of 8 (normal values: $11.08 \pm 9.47\%$). The performance of the patient was assessed as normal.

MRI acquisition: 23 years later, we performed, with the patient's consent, a brain MRI including T1 and T2 weighted sequences, diffusion, and 3D high resolution (0.9 millimeters isotropic voxel) T1 with gadolinium injection. MR imaging was performed on Philips Intera 1.5-T Tesla MR system (Philips Medical Systems, Erlangen, The Netherlands) with a standard head coil. Localizing sagittal T1-weighted images of the brain were obtained initially, followed by axial T2-weighted images. Diffusion-weighted imaging comprised an echoplanar spinecho sequence, with the following parameters, TR = 4247, TE = 95, EPI factor = 77, field of view (FOV) = 230 mm, slice thickness = 5 mm, slice gap = 1 mm, number of excitations = 1, matrix = $77 \times 256$, number of slices = 22, acquisition time = 30 seconds. The images in DWI were acquired for values of $b$ (diffusion gradient factor) equal to 0 and 1000 s/mm². An isotropic image was constructed in real time, pixel by pixel, as an average the signal intensities of three orthogonal directions. ADC maps were then calculated from the diffusion-weighted images.

3D reconstructions were post-processed by bio-imaging (Bio-imaging Technologies SAS, France).

We also performed a brain MRI with the same sequences except gadolinium injection in a 55-year-old healthy female of the same height.

![Figure 1](image-url)  
**Figure 1** Frontal lobe evolution on CT scan (1984) and Brain MRI (2007). Twenty-three years after the onset, bilateral prefrontal atrophy is showed contrasting with the non-atrophy of the precentral gyri (inverted omega shape, stars).
Results

Pons

The T2 axial weighted images show a hypointensity in the ventral part of the pons while the dorsal and lateral parts of the tegmentum of the pons and the midbrain above are spared. Those images correspond to the pontine stroke consecutive to the initial thrombosis of the basilar artery. The cavity affects the ventral part of the pons, also called basilar portion, where normally the bundles of motor fibers are located (corticopontine, corticobulbar, and corticospinal) together with the transversely oriented pontocerebellar fibers and the widely scattered pontine nuclei that give rise to them. The images show a repermeabilisation of the basilar artery, which appears as a flow void on T2 weighted images (Fig. 2A) and enhanced on T1 weighted images after contrast injection.

Cerebellum

The T2 axial weighted images display an atrophy of both hemispheres and cerebellar vermis. Atrophy predominantly affects the culmen, declive, and uvula. It also affects the middle cerebellar peduncles, which show no abnormal signal on T2 weighted images. The superior peduncles are less atrophic while the inferior peduncles are spared (Fig. 2A).

Medulla oblongata

Compared to the control, the T2 axial weighted images show a complete disappearance of the prominence of medulla oblongata pyramids, corresponding to the corticospinal tract degeneration and atrophy. In contrast, the posterior portion of medulla oblongata is spared, particularly the olivary bodies, which appear as smooth oval prominences of the ventrolateral surface of the medulla oblongata and correspond to the olivary nuclei (Fig. 2).

Spinal cord

Compared to the control, the T2 axial weighted images show an atrophy of the cervical spinal cord with a square aspect related to the atrophy of the anterolateral funiculus in the spinal cord.

Mesencephalic areas

Compared to the control, the T2 axial weighted images show an enlargement of the interpeduncular cisterna in favour of the internal part of the cerebral peduncle atrophy while the mesencephalic tegmentum is preserved (III, IV nucleus).

Corticospinal tract

Compared to the control, the diffusion axial weighted images performed in the lateral encoding direction show a loss of the normal hypersignal of the corticospinal tract in the middle part of the cerebral peduncles, the posterior part of the internal capsules and the corona radiata of both hemispheres (Fig. 3).

Basal ganglia

Compared to the control, the T2 axial weighted images show a normal morphological aspect of both pallidum and striatum while a bilateral and symmetric slight hypersignal is observed in the posterior and lateral parts of the thalami.

White matter

No hypersignal was observed on T2 weighted images in frontal, parietal and temporal white matter. Contrary to the genu and posterior parts of the internal capsules, the anterior part was hardly detectable on conventional T2 weighted images.

Cortical areas

Compared to the control, the T2 axial and sagittal weighted images showed a bilateral and symmetrical atrophy of the frontal cortex contrasting with the morphological integrity of the primary motor cortex and temporal, parietal, insular and occipital cortices. Moreover, the occipital lobes appeared slightly enlarged compared to the control (Fig. 2A). This atrophy was limited to the dorsomedial prefrontal areas (Brodmann areas 8, 9 and dorsal 46) although the frontopolar and orbitofrontal areas (BA 10, 11, 12), the anterior cingulate area (BA 32) and the corpus callosum were morphologically normal (Figs. 1 and 2).

Discussion

We give here a thorough MRI study of the brain structures, especially the frontal lobe in a long-standing de-efferentation due to a 23-year locked-in syndrome (LIS). Plum and Posner first reported LIS as a clinical entity in 1966 [1]. The clinical picture is that of a patient who is essentially conscious, has cognition, but is unable to communicate with the outside world due to quadriplegia and lower cranial nerve lesions. It was redefined, in 1986, as quadriplegia and anarthria with preservation of consciousness [8].

As in previous reported patients, the vascular ischaemic lesion is located in the anterior part of the pons consecutive to the obstruction of the basilar artery. In our case, this obstruction was consecutive to a dissection of the vertebral artery with a secondary repermeabilisation. Vascular disease is one of the most frequent causes of LIS [9]. Some areas in the mid-brain are spared, which explains the preservation of some functions, particularly the dorsal pons (sensory pathways, consciousness), the cranial nerve nuclei I to IV, and the mesencephalic tegmentum, where the oculomotor and trochlear nuclei are located (preservation of the eye movements).

Quadriplegia is due to the interruption of the corticospinal tracts up to the decussation (pons). In the ventral pons, bundles of motor fibers—corticobulbar, corticopontine, and corticospinal—continue their descent from the basis pedunculi. Secondary degeneration of those long tracts has been observed in medulla oblongata and spinal cord injury [10]. In our observation, long-term anatomic evaluation of the wallerian degener-
Arnold tract degeneration

Figure 2  Comparison of different MRI sequences (SE T1 and SE T2) and planes (sagittal and axial) between the chronic LIS patient and a healthy subject matched for age and sex. Sagittal T1 weighted image. Parasagittal slice displayed a cerebellar atrophy predominantly affecting the culmen, decline and uvula; a selective atrophy is depicted in the dorsomedial prefrontal cortex while the precentral gyrus, the cingulum and the corpus callosum are spared. Note that the head position is not the same because of tracheotomy and posterior neck muscles atrophy (2A). T2 axial weighted image of the mid-brain and upper spinal cord displayed a porencephalic cavity in the ventral pons, the repermeabilisation of the basilar artery (flow void on T2 weighted image, enhance after gadolinium injection) and a middle cerebellar peduncles and cerebellar hemispheres atrophy. The dorsal pons and the midbrain above the pons are spared (2B). T2 axial weighted image of the medulla oblongata displayed an atrophy of the cerebellar hemispheres and a disappearance of the pyramids reliefs (black arrows) whereas olivar areas appeared normal (white arrows) (2C).

ation of the corticospinal tracts (below the pons) leads to a characteristic medulla oblongata square form due to the disappearance of the normal relief of the pyramids (Fig. 2).

Up to the pontic lesions, the corticospinal tracts do not demonstrate atrophy. The cerebral peduncles, the posterior limb of the internal capsules and the precentral gyrii seem to be spared. However, on the diffusion image, a tech-
Figure 3  Comparison of diffusion weighted images in the “lateral encoding direction” between a chronic LIS patient and a healthy subject matched for age and sex. In the healthy subject, the corticospinal tract is normally visualized in hypersignal in this encoding direction (perpendicular to the corticospinal tract). With our patient, the corticospinal tract hypersignal has disappeared in the corona radiata (3A), in the posterior limb of the internal capsules (3B) and at the pontic level (3C).
Arnold tract degeneration

In many patients with LIS, horizontal eye movements and blinking are the only preserved movements, and hence, their only means of communication and cognitive preservation. In our case, a part the dorsomedial and part of the dorsolateral prefrontal areas, all cortices, the corpus callosum and the anterior cingulate cortex are spared. The anterior cingulate gyrus appears to play a role in a wide variety of autonomic functions, as well as rational cognitive functions, such as reward anticipation, decision-making, empathy and emotion. Already, in a report on two patients with chronic LIS, more recent study showed that patients with LIS do, in fact, present moderate and selective cognitive disorders, which is evinced by the performance of relatively complex tasks such as complex sentence comprehension, mental calculation and problem solving [11]. As for our patient, there was no evidence of behaviour modification, no loss of emotion or empathy, and no decision-making deficit as assessed by the WCST.

In our study, we observed a discrepancy between the selective atrophy of the dorsolateral and the dorsomedial prefrontal areas and the spared precentral area and other parts of prefrontal areas that are highly cognitive regions. The vascular aetiology, in our case, could not explain this selective prefrontal atrophy. It could have been different if the LIS had been caused by a traumatic injury. Many studies (post-mortem and in vivo) suggest an anatomic vulnerability of prefrontal areas [12—18]. Nevertheless, the contrast between the atrophy of some part of the prefrontal areas and the others preserved prefrontal areas and the other cortices could not only be explained by an age-related increased vulnerability. The lesser vulnerability and possible reorganisation processes of the primary motor centres [9,19] could explain the non-atrophy of the precentral gyri. Our hypothesis is that the prefrontal atrophy is secondary to the degeneration of pontopontic fibers in relation to the ventral pontic destruction. The cortico-pontocerebellar system is known to be one of the largest projection systems in the primate brain, but in the human brain, the location of the projection remains unclear. In 1838, the German anatomist Friedrich Arnold (1803—1890) in his “Tabulae Anatomicae quas ad Naturam Accurate Descriptas” first depicted the frontopontine tract (now known as Arnold’s prefrontopontocerebellar way), which extends “from the frontal cortex through the anterior limb of the internal capsule via the medial part of the cerebral peduncle to the pons” [20]. The precise location in the prefrontal cortex was not described. This cortico-pontocerebellar pathway is quantitatively the most important route by which the cerebral cortex can influence the cerebellar cortex. The corticopontine projection carries information, which the contralateral cerebellum uses to participate in the preparation, the initiation and execution of movements. Both middle cerebellar peduncles, which are normally a massive bundle of fibers, appear atrophic, manifesting a degeneration of transverse pontocerebellar fibers. In a recent study, two cases of ventral pontine infarct with wallerian degeneration affecting the middle cerebellar peduncle have been described [21].

Little is known of the precise anatomical organization of cortices implicated in the human cortico-pontocerebellar system. Previous principal findings of those cortices included prefrontal, frontopolar and orbitofrontal cortices (areas 4, 6, 8, 9, 10, 11, 12), cingulate cortex (areas 23, 24, 25, 32) and parietal cortices [22]. In our observation, parietal and temporal cortices were also preserved in a morphologic point of view. The so-called bundle of Türck or temporo-pontine tract seems in fact to have never existed [23]. Another explication could be related to the lateral position of the temporo-pontic fibers inside the pons, which is preserved in our observation (Fig. 4).

Diffusion tensor imaging and tractography are not being robust enough to accurately describe the cortical pontine projections. Injection in the pons demonstrated retrograde labelled neurons in areas 6 and 8 and to a lesser extend in the lateral and dorsomedial prefrontal cortex [24] and in area 8 and 9 [25]. A relatively large prefrontal contribution to the human cortico-pontocerebellar system was found in the cerebral peduncle [26]. Using functional connectivity MRI, low-frequency fluctuations in MR signal in the dentate nucleus correlated with signal fluctuations in the cerebrocortical regions, including the parietal and frontal sites, with prominent coherence in dorsolateral prefrontal cortex [22]. Schmahmann studied the pontine projections using the autoradiographic technique in the rhesus monkey. Pontine projections were located in the dorsolateral prefrontal convexity (8Ad, 9/46d, 10) and in the medial prefrontal convexity [27]. The case we described is unique. Our data support the hypothesis of a highly selective prefrontal contribution of the cortico-pontocerebellar pathway with prominent dorsomedial prefrontal areas (Brodmann areas 8, 9 and dorsal 46).

Conflicts of interest statement

The authors declare no conflicts of interest.
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