Vertical gaze palsy and selective unilateral infarction of the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF)

J Bogousslavsky, J Miklossy, F Regli, R Janzer

Abstract

We report a clinico-pathological correlation study in a patient with basilar artery thrombosis, who developed tetraplegia and combined up- and downgaze palsy involving voluntary saccades and visually-guided movements, but sparing the oculocephalic responses. At necropsy, apart from bilateral infarction in the basis pontis, there was a single unilateral infarct selectively destroying the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF) on the right. The posterior commissure and its nucleus, the nucleus of Cajal, the nucleus of Darkschewitsch and the pontine tegmentum were spared. We suggest that the unilateral riMLF lesion may have disrupted bilateral upgaze excitatory and inhibitory inputs and unilateral downgaze excitatory inputs. The functional anatomy of inhibitory and excitatory vertical gaze circuitry, which remains speculative, may explain why a unilateral lesion of the upper midbrain tegmentum may be sufficient to generate an upgaze palsy or a combined up- and downgaze palsy, while an isolated downgaze palsy requires bilateral lesions.

It is well known that vertical gaze palsy is related to mesencephalic dysfunction.[1 2] More recently, the critical area for the genesis of up- and downward saccades in the monkey and in humans has been found to be located dorsomedial to the anterior pole of the red nucleus, in an area now called the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF)[3 4]. Other upper midbrain structures implicated in vertical gaze include the posterior commissure, the interstitial nucleus of Cajal and the nucleus of Darkschewitsch.[5] Classically, upgaze palsy has been related to uni- or bilateral upper midbrain lesions, while a bilateral lesion is required to give rise to downgaze palsy.[5 6] However, the respective role of the riMLF, posterior commissure, nucleus of Cajal, nucleus of Darkschewitsch, and related structures has remain difficult to assess in humans, in the absence of case reports with selective involvement of one or the other of these structures.

Our report of a patient with combined up- and downgaze palsy in association with an upper midbrain infarct limited to the riMLF on the right side may provide further insight in the understanding of the control of vertical gaze.

Department of Neurology* and Division of Neuropathology† Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland
J Bogousslavsky*
J Miklossy†
F Regli*
R Janzer†

Correspondence to:
Dr Bogousslavsky, Department of Neurology, CHUV, 1011 Lausanne, Switzerland.

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Case report

A 60 year old housewife who was a smoker had been investigated for ten years for arterial hypertension, diabetes mellitus and elevated blood cholesterol. Three weeks before admission, she experienced transient dysarthria and dizziness and the day before had been unable to stand and experienced tingling in the left hand. One day later, she suffered acute rotatory vertigo with vomiting, diplopia, dysarthria, and left-sided weakness and numbness. On admission, the patient was well-oriented in time and place but had severe dysarthria. Blood pressure was 140/85 mm Hg. The visual fields were normal. Eye movements were normal. The pupils could not be assessed, because of previous cataract operations. She had a slight lower facial paresis on the left. The remainder of the cranial nerves were normal. She had a moderate left hemiparesis with decreased sensation for temperature and pain. The upper limb showed dysmetria and dysdiadochokinesia. Over 24 hours after admission, the patient progressively worsened and developed a complete left hemiplegia, despite intravenous heparin therapy (30 000 Iu/24 h). Progressive weakness then developed on the right, and four days later she had a spastic tetraplegia with facial diplegia and severe lower cranial nerve palsy. The clinical picture showed a typical locked-in syndrome, except for the horizontal eye movements which were unimpaired when tested for voluntary and pursuit gaze. The patient could open and close her eyes on command, but there was a complete vertical gaze palsy for voluntary and pursuit movements. Bedside vertical optokinetic testing with a drum showed no response, but the vertical oculocephalic manoeuvre elicited a full upward and downward response. This state remained unchanged for four months. The patient then developed palpebral ptosis and adduction weakness in the right eye. It became more difficult to communicate with the patient using her preserved eye movements. At the same time, the tetraplegia became flaccid, the patient developed purposeless chewing movements, and her weight dropped by 30 kg. She died six months after admission.

Laboratory investigations

Brain CT was checked three times and showed a right occipital, left lenticular and right pontine infarcts. Bilateral vertebral digital arterial angiography ten days after admission showed progresive stenosis of the basilar artery from the last part of the middle third, with occlusion of the distal third. Brainstem auditory evoked

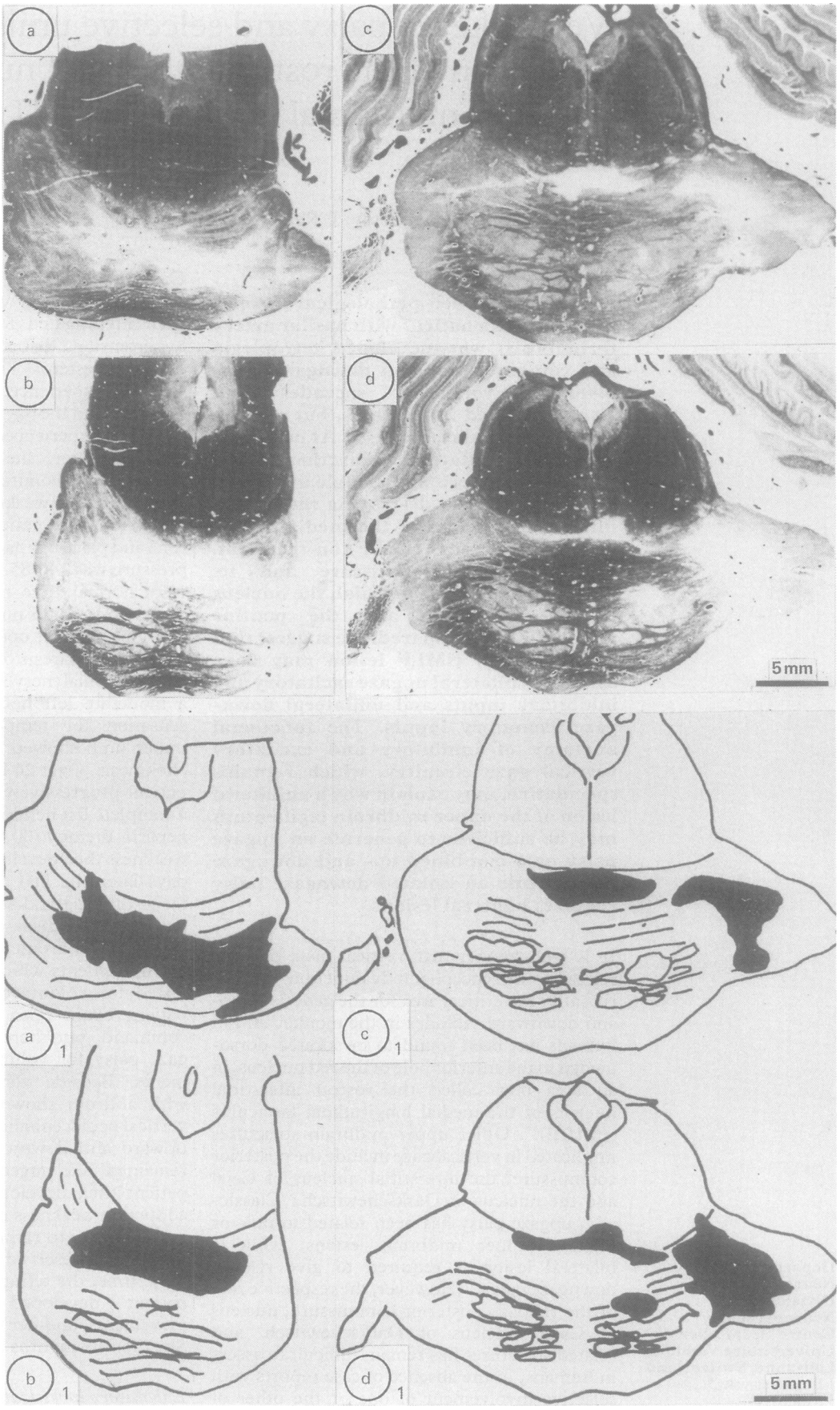

Figure 1 Paraffin sections stained for myelin (Loyez), through the pons at four different levels (A: mesencephalic-pontine junction; B: upper pons; C and D: midpons), showing the extent of the bilateral cystic infarction. A1, B1, C1 and D1 are schematic representations of the lesion at the same levels.

potentials showed no abnormality when performed three and four months after admission. ECG and standard blood tests were normal.

Neuropathological findings

The brain was fixed in 10% formalin for three weeks. After macroscopical examination, the brain was cut in 8 mm coronal slices. Blocks were taken from the left striatum, the left occipito-temporal, the right occipital region and from the cerebellum. Ten μm paraffine sections were stained with hematoxyline-

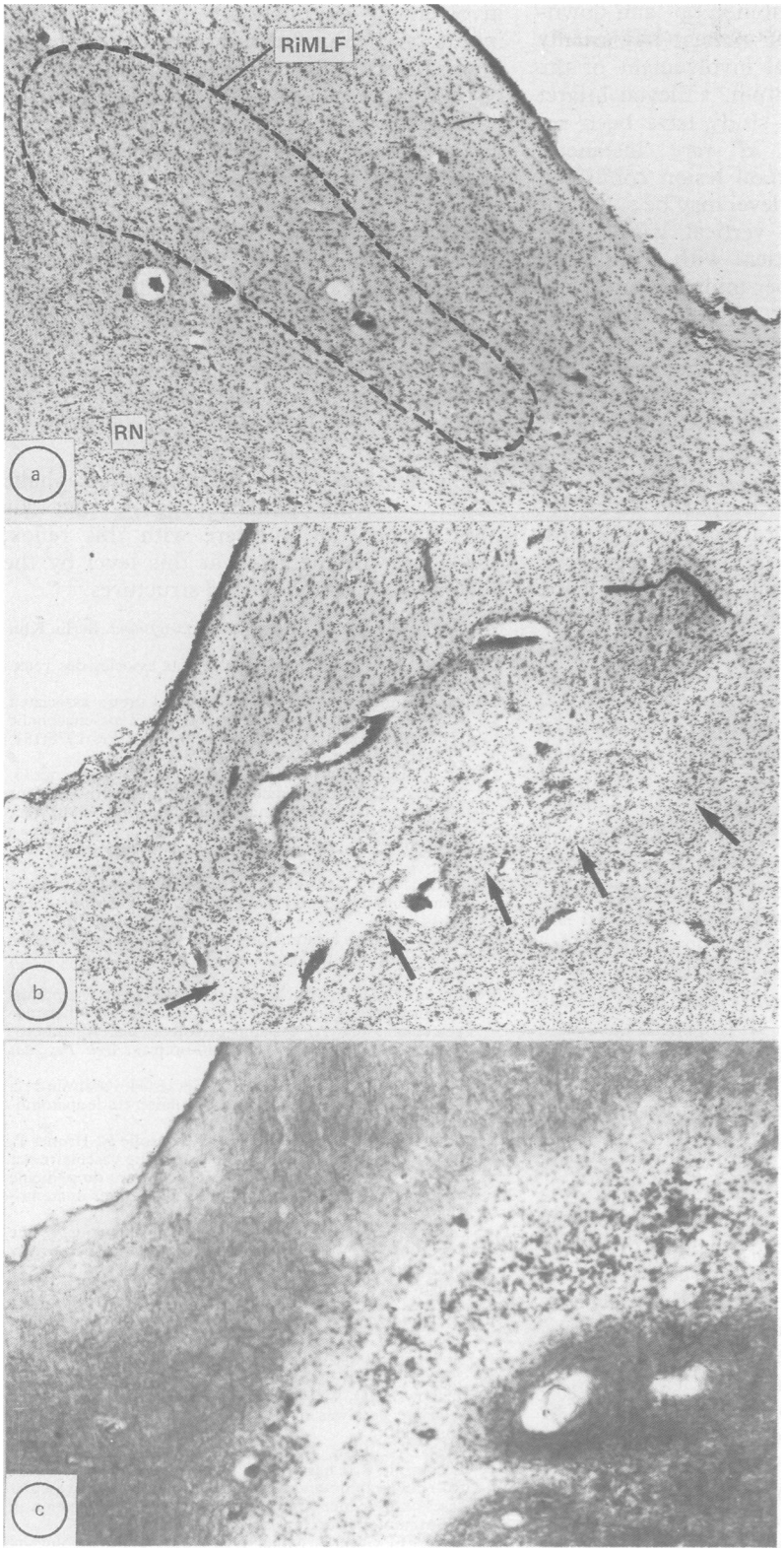

Figure 2 a: Coronal section of the upper midbrain at the level of the posterior commissure and demonstrating the localisation of the spared left riMLF (dashed line). Nissl stain. Magnification: 30 ×. b: Same section on the right side, showing the riMLF entirely destroyed by the infarct. Arrows point to the inferior limit of the lesion. Same staining and magnifications as A. c: Coronal section adjacent to B, stained with Sudan black showing clearly the clearly defined infarct in the right riMLF. Magnification: 30 × riMLF = rostral interstitial nucleus of the medial longitudinal fasciculus; RN = red nucleus.

eosine, cresyl violet, luxol fast blue-Van Gieson, periodic acid-Schiff and Loyez stains. Forty μm frozen sections were cut from blocks of the same regions and were stained with Oil red 0 and Sudan black. Ten μm serial paraffine sections from the mesencephalon, pons and superior part of the medulla oblongata were stained alternatively with hematoxyline-eosine and Loyez stains. Forty μm frozen serial sections from blocks of the thalamus and upper midbrain on both sides were stained with Oil red 0 and Sudan black.

The brain weighed 1290 g. There was no sign of oedema or atrophy. The circle of Willis showed severe atherosclerosis. The middle third of the basilar artery was totally occluded by an organised, recanalised thrombus which extended into the rostral segment of the artery. In the examination of the cerebral hemispheres there was revealed a small old cystic infarct (1·5 cm diameter) in the deep territory of the left middle cerebral artery destroying the supero-lateral part of the striatum and involving the anterior-superior part of the internal capsule, and an old infarct in the territory of the right posterior cerebral artery destroying the posterior part of the lingual and fusiform gyri.

The most important lesion was an infarct in the territory of the basilar artery, the appearance of which corresponded to the duration of the clinical history. The infarct involved large parts of the ventral pons, but the tegmentum of the pons was completely spared (fig 1). The medial longitudinal fasciculus, the trochlear and abducens nuclei and their fibres, as well as the paramedian pontine reticular formation (PPRF) were intact on both sides. The caudal pons, medulla oblongata and cerebellum did not show any foci of infarction.

At the meso-diencephalic junction, there was an infarct at the level of the central mesencephalic grey, and the right rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF) was damaged (fig 2). The nucleus of Darkschewitsch, the interstitial nucleus of Cajal, the nucleus and fibres of the posterior commissure as well as the nuclei of the pretectal region were completely spared. On the left side, the mesencephalic tegmentum was entirely spared.

A more recent minute focus of infarct was found in the supero-lateral part of the right oculomotor nuclear complex, involving the rostral part of the dorsal, ventral and intermediate columns.

Discussion

Our patient had a severe infarct of the ventral pons due to basilar artery thrombosis. The pontine tegmentum was completely spared, which explained the normal horizontal eye movements. On the other hand, a small focus of infarction was found in the mid-brain tegmentum on the right, which selectively involved the riMLF, and corresponded to the vertical gaze disturbances. A more recent small infarct involved part of the right oculomotor nucleus on the right, explaining the palpebral ptosis and adduction weakness in the right eye, which developed shortly before death. Thus, although our patient had other ischaemic lesions than that in the upper midbrain tegmentum, it is the first case in which vertical gaze abnormalities can be correlated to selective unilateral riMLF infarction.

The syndrome of combined up- and downgaze palsy shown by our patient has usually been related to bilateral involvement of the upper midbrain tegmentum.[5 6] Eleven infarct cases with pathological study have been reported.[4 7-16] However, in rare instances, it appears that a unilateral lesion confirmed at necropsy at the same level may be sufficient to generate combined vertical gaze palsy. Dereux[17] reported a patient with a unilateral lesion involving the upper midbrain and periaqueductal area. Garcin *et al*[18] reported the case of a woman aged 65 with an upper brainstem infarct that was limited to the left side, who had a combined vertical gaze paresis, though "slight upward and downward movements were still possible". Collier[19] described a woman aged 49 with up- and downgaze palsy and a left thalamo-mesencephalic haemorrhage. Molnár[20] reported a man aged 72 with upgaze palsy and "limitation of downgaze" with a left paramedian thalamo-mesencephalic infarct. Leigh and Zee[21] reported a 38 year old woman with upgaze palsy and decreased downward saccades velocity and smooth pursuit with a left thalamic-midbrain haemorrhage. More recently, Ranalli and Sharpe[22] reported a 64 year old man who had a right paramedian upper brainstem infarct and palsy of upward saccades, decreased amplitude and velocity of downward saccades, decreased gain and amplitude of vertical smooth pursuit and vestibulo-ocular response, and inverted Bell's phenomenon on prolonged lid closure. In the first five cases, the neuropathological study did not include microscopic details, but the region of the posterior commissure and riMLF was involved in all instances. In the sixth case, the right riMLF, nucleus of Darkschewitsch, and part of the nucleus of Cajal and of the nucleus of the posterior commissure were involved, but the posterior commissure was spared. In our patient, the right riMLF was selectively involved in the upper midbrain, while the posterior commissure and its nucleus, the nucleus of Cajal and the nucleus of Darkschewitsch were completely spared.

Though our study suggests that selective involvement of riMLF on one side may generate a combined vertical gaze palsy, the explanation of this remains unclear. Cases of unilateral midbrain lesion with upgaze[15 23-30] or combined up- and downgaze[17-22] palsy have been reported, but there is no single case with pathological verification in which downgaze palsy was due to a unilateral lesion. In patients with isolated downgaze palsy and an apparently unilateral infarction on MRI[31] a small contralateral lesion cannot be excluded.

It is possible that inhibitory as well as excitatory upgaze fibres from the riMLF on one side may decussate in the posterior commissure and pass through the contralateral riMLF on their way to the oculomotor nuclear complex. On the other hand, there is no experimental or clinical evidence that downgaze fibres decussate in the posterior commissure.[5 20] This decussation is probably lower in the midbrain, close to the oculomotor nuclear complex.[15 32] The combined involvement of bilateral upgaze inhibitory inputs and unilateral downgaze excitatory inputs from a unilateral riMLF lesion may thus be sufficient to generate downgaze palsy, because the uninvolved contralateral downgaze inputs cannot compensate. Moreover, the preservation of contralateral downgaze inputs explain why downgaze was usually only paretic, in contrast to complete upgaze palsy, in the previously reported patients with a combined vertical gaze palsy and a unilateral lesion.

On the other hand, this would also explain why downgaze palsy from a unilateral riMLF involvement may not occur without associated upgaze palsy, because bilateral upgaze excitatory and inhibitory inputs are involved concomitantly within the riMLF.

The sparing of the vertical oculocephalic response in our patient suggests that the riMLF does not interfere with this reflex, which may be mediated at this level by the nucleus of Cajal and related structures.[22 30]

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