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Clinical characteristics in patients with oculomotor paralysis caused by isolated midbrain infarction

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Abstract

Introduction: *The aim of the study was to investigate the clinical characteristics of isolated oculomotor paralysis (OP) cases caused by pure midbrain infarction (MI) with pupil sparing.*

Material and methods: *Patients with pure MI and pontine infarction (PI) at our hospital were included in this study. We compared the blood pressure and lipid levels between the two groups. And the clinical data and imaging features were summarized.*

Results: *In total, 33 and 35 patients were included in the MI and PI groups, respectively. There was no significant difference in the distribution of age (64.9 ±10.0 vs. 65.1 ±10.8 years, p = 0.927) and males (84.8% vs. 74.3%, p = 0.282) between the MI and PI groups, respectively. The pure MI group had a comparable level of serum lipoprotein and cardiovascular risk factors compared with the PI group except for a lower proportion of hypertension (57.6% vs. 85.7%, p = 0.010). The majority (72.7%) of culprit lesions in the pure MI group was located in the paramedian area of the midbrain, and the ocular muscle palsies mostly involved the medial rectus (75.8%).*

Conclusions: *The Chinese patients with OP caused by pure MI were mainly characterized with rapidly progressive symptoms, multiple cerebrovascular risk factors, and typical MRI signs. Further efforts should be made in the differential diagnosis of this atypical midbrain syndrome.*

Key words: *pure midbrain infarction, isolated oculomotor paralysis, pupil sparing, imaging features; clinical study.*

Introduction

Oculomotor paralysis (OP) is a common and clinically important neuro-ophthalmologic sign characterized by diplopia, ptosis, and pupillary dilation, and its aetiology is diverse and complex [9]. Many different factors have been reported to cause OP, such as diabetes, aneurysms, tumours, cerebral infarction, and subarachnoid haemorrhage [13,17]. The oculomotor nerve nucleus located in the anteromedial region of midbrain sends out the oculomotor nerve fibres forwards, leaves the brain stem located on the anteromedial region of the midbrain, leaves the brainstem at the medial aspect of the interpeduncular fossa, passes through the lateral wall of the cavernous sinus, and enters the superior orbital fissure [20]. Due to the long columnar distribution of oculomotor nerve nuclei, when the lesion is relatively limited, it may present as complete paralysis of the extraocular muscles innervated by the ipsilateral oculomotor nerve, while the intraocular muscles innervated by the parasympathetic nerve fibres are not affected, that is, there is isolated OP without the pupil involved [3].

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The arteries of the midbrain originate from the posterior cerebral artery, basilar artery, superior cerebellar artery, and anterior choroidal artery, which are rich in blood supply. Consequently, infarcts confined to the midbrain are clinically uncommon. Pure midbrain infarction (MI) incidence is about 0.6% in patients with ischemic stroke but it could lead to serious consequences and worse prognosis [7]. Patients with pure MI might present with various vascular complications that affected the function and life quality, including Weber syndrome, Benedikt syndrome, and Claude syndrome [18], as well as the rare Wernekink commissure syndrome [22] and incomplete midbrain syndromes such as unilateral ptosis, isolated inferior rectus palsy, and vertical supranuclear gaze palsy [4,14,15,23]. Rarely, isolated unilateral oculomotor paresis without any significant neurological symptoms is brought on by a pure midbrain stroke, imitating cranial mononeuropathy III, or injury to the oculomotor (third cranial) nerve. In these situations, the oculomotor fascicles are affected by lesions in the ventromedial area of the midbrain. However, there are few reports about the OP with pupil avoidance due to pure MI. Therefore, we conducted a study to investigate the clinical characteristics of isolated OP due to pure MI and compare them with those in patients with pontine infarction (PI).

Material and methods

Study design and population

This study was a single-centre, retrospective study. Consecutive patients with acute cerebral infarction involving isolated midbrain or pons who were treated at our institution between May 2018 and August 2022 were screened for eligibility. Patients would be selected if they 1) met with the diagnostic criteria of cerebrovascular diseases in China in 2019 [5]; 2) had an onset of ≤ 7 days; and 3) were confirmed by brain magnetic resonance imaging (MRI) to have culprit lesions confined to the midbrain or pons. Exclusion criteria were as follows: 1) diseases complicated with other brain parenchymal damage, such as central nerve demyelination disease, cerebral haemorrhage, intracranial infection, brain tumour, brain trauma, intracerebral aneurysm, and diabetic oculomotor nerve palsy; 2) accompanied by new cerebral infarction lesions outside the midbrain or pons; 3) severe heart, lung, liver, kidney and other organ dysfunction; 4) advanced malignant tumour; and 5) incomplete data. After onset of the disease, all patients were then given routine medical treatment according to their severity and clinicians' discretion. Patients were divided into two groups according to the MRI examination: the pure MI group and PI group. The present study was conducted in accordance with the Declaration of Helsinki and the protocol was approved by the ethics committee of our hospital. The requirement of informed consent was waived due to the retrospective design of this study.

Data collection

Clinical data mainly included the gender, age, previous medical history such as stroke, hypertension, diabetes mellitus, cardiac diseases (including coronary heart disease, atrial fibrillation, and valvular disease), hyperlipidaemia, smoking, and alcohol consumption. All patients underwent laboratory tests such as fasting blood glucose, total cholesterol, triglyceride, high-density lipoprotein cholesterol and low-density lipoprotein cholesterol, blood cell count, clotting time, urine and bowel routine, indicators of liver and kidney function, and electrolyte. Carotid ultrasound, transcranial magnetic Doppler ultrasound, echocardiography, head and neck computed tomography angiography (CTA) and head MRI images were extracted from the imaging database. Clinical characteristics were collected from the electronic medical record, including motor and sensory disorders, eye movement palsy, bulbar palsy, medication regimen and disease progression.

MRI imaging

All patients underwent brain scanning using 3.0T MRI (Magnetom Verio, Siemens Healthineers, Germany) during hospitalization. MRI imaging sequences included T1-weighted imaging (T1WI) and T2-weighted imaging (T2WI), fluid attenuated inversion recovery (FLAIR), diffusion weighted imaging (DWI), and 3-dimensional time-of-flight (3D TOF) magnetic resonance angiography (MRA). According to the blood supply areas of the midbrain or pons artery, the midbrain can be divided into the anteromedial region, anterolateral region, lateral region, and dorsal region [1,10]. Pons were divided into anterior medial and anterolateral pons artery supply areas, lateral pons artery supply areas, and posterior pons artery supply areas [6].

Statistical analysis

All statistical analysis was performed using the software program SPSS 20.0 (IBM, Chicago, USA). Histograms and Q-Q plots were used to examine whether data followed a normal distribution. The continuous variables of normal distribution were expressed as mean ± standard deviation and compared using the Student's *t*-test between two independent groups. The continuous variables of non-normal distribution were expressed as median (interquartile range) and compared using the Mann-Whitney *U* test. The categorical variables were expressed as counts (percentages)

and compared using the chi-square test. A two-tailed p value of < 0.05 was considered statistically significant.

Results

General characteristics

In total, 33 and 35 patients were included in the MI and PI groups, respectively. The average age was 64.91 ±9.97 years in the pure MI group and 65.14 ±10.83 years in the PI group, with no significant difference between the two groups (p = 0.927). There was a higher proportion of hypertension in the PI group than the MI group (85.7% vs. 57.6%, p = 0.010). The difference of the proportion of atrial fibrillation between the two groups reached a borderline statistical point (12.1% vs. 0.0%, p = 0.050). Overall, there were no significant differences in the distribution of age, sex, and other cerebrovascular disease risk factors between the isolated MI group and PI group, as shown in Table 1.

Comparison of lipid levels between two groups

In the pure MI group, the blood triglycerides (TG) level was 1.78 ±1.02 mmol/l, the total cholesterol (TC) level was 4.88 ±0.95 mmol/l, the high density lipoprotein (HDL) cholesterol level was 2.86 ±0.75 mmol/l, and the low density lipoprotein (LDL) cholesterol level was 1.27 ±0.23 mmol/l. In the PI group, the blood TG level was 2.14 ±2.05 mmol/l, the TC level was 5.23 ±1.40 mmol/l, the HDL level was 2.97 ±1.13 mmol/l, and the LDL level was 1.24 ±0.20 mmol/l. The results showed that the TC level (p = 0.237), the TG level (p = 0.365), the HDL level (p = 0.640), and the LDL level (p = 0.500) were comparable between the two groups (Table I).

Clinical characteristics of the pure MI group

The clinical features of 33 pure MI patients were summarized in Table II. Causative lesions were located strictly in the paramedian area of the midbrain, which was supplied by perforators from the posterior cerebral artery (P2 segment). In all 33 patients, ocular muscle palsies did not involve all of the muscles innervated by the oculomotor nucleus, and the pupillary sphincter (SP) and the inferior oblique (IO) were selectively spared. Of the 33 infarcted patients, 25 were affected with the medial rectus (MR) manifesting as adduction palsy, 11 were affected with the inferior rectus (IR) and the superior rectus (SR) manifesting as elevation or depression palsy. And 4 were also affected with the levator palpebrae (LP) manifesting as ptosis.

Discussion

The present study investigated the clinical characteristics of isolated OP patients caused by pure MI with pupil sparing. The main findings are as follows: 1) there was no significant difference in general characteristics (e.g., age, gender, cardiovascular risk factors) between the isolated MI group and PI group except for hypertension; 2) the pure MI group had a comparable serum level of TG and lipoprotein to those in the PI group; 3) patients with isolated OP mainly presented with symptoms with acute onset and rapid progression, and they often had multiple cerebrovascular risk factors with typ-

Table I. General data of the MI group and PI group (N = 68)

Index	MI group (n = 33) Mean ±SD or n (%)	PI group (n = 35) Mean ±SD or n (%)	P-value
Age (years)	64.9 ±10.0	65.1 ±10.8	0.927
Male	28 (84.8)	26 (74.3)	0.282
Hypertension	19 (57.6)	30 (85.7)	0.010
Diabetes mellitus	15 (46.9)	13 (39.4)	0.543
Hyperlipidaemia	18 (54.5)	19 (57.6)	0.804
Smoking	14 (48.3)	12 (38.7)	0.455
Drinking	11 (33.3)	9 (25.7)	0.491
Atrial fibrillation	4 (12.1)	0 (0.0)	0.050
Coronary artery disease	3 (9.1)	4 (11.4)	1.000
Previous cerebral infarction	8 (24.2)	10 (28.6)	0.686
TC (mmol/l)	4.88 ±0.95	5.23 ±1.40	0.237
TG (mmol/l)	1.78 ±1.02	2.14 ±2.05	0.365
HDL (mmol/l)	2.86 ±0.75	2.97 ±1.13	0.640
LDL (mmol/l)	1.27 ±0.23	1.24 ±0.20	0.500

MI – midbrain infarction, PI – pontine infarction, TC – total cholesterol, TG – blood triglycerides, HDL – high density lipoprotein, LDL – low density lipoprotein

ical signs in MRI imaging. To the best of our knowledge, this is the first study to report the clinical features of this subgroup of Chinese patients. The findings can translate into clinical benefits that neurologists should pay more attention to the differential diagnosis of this atypical midbrain syndrome based on these characteristics including symptoms and MRI results.

The long duration of diabetes mellitus, poor glycaemic and lipid control, obesity, and comorbidities are important risk factors for the complications of OP [20]. Isolated MI characterized by OP with pupil sparing needs to be distinguished from diabetic OP. Diabetic lesions tend to cause secondary ischemic and hemodynamic damage to the somatomotor fibres in the inner layer of the oculomotor nerve but have no major effect on the parasympathetic fibres in the dorsal midline against the medial surface. Consequently, the main characteristics of diabetic OP are poorly controlled blood glucose with unilateral extraocular muscle involvement and no pupillary involvement. All 33 patients reported in this paper showed partial extraocular muscle paralysis, without pupils being involved, which should be differentiated from diabetic OP. However, the OP symptoms in these 33 patients were acute onset with rapid progress, and all of them had risk factors for cerebrovascular disease. Combined with the new midbrain infarct lesion suggested by cranial MRI, the final diagnosis was OP caused by acute MI, and diabetic OP was excluded, similar to previous reports of OP caused by MI with no pupillary involvement [20,21].

It has been reported that insufficient blood supply due to arterial stenosis caused by anatomy and syndromes (AS) is the main pathological factor for posterior circulation ischemia [8,18]. Low density lipoprotein, a famous bad cholesterol, has a direct effect on promoting the formation of AS, therefore it is a potential risk factor for AS. The increase in serum TC and TG are also risk factors for AS [2]. The incidence of AS increases with higher serum TC, TG, and LDL levels. Pontine infarction, as the main type of posterior circulation ischemia, involves damage of more complex large vessels [2,8]. While pure MI injury is relatively limited and very rare, and the main responsible vessel is the perforator artery, most of which is arteriole disease. The lower lipid levels of 33 patients in the MI group suggested that their related vascular damage might be less severe. However, the difference was statistically insignificant.

Studies have shown that the oculomotor nerve tracts in the midbrain can be divided into cephalic, intermediate, and caudal tracts, of which the cephalic tract innervates IR and SP and extends medially to the head of the red nucleus, while the intermediate tract innervates MR and IO, and the caudal tract innervates SR and LP [19], which are arranged in an inside-out distribution pattern in the midbrain cross-section as follows: SP, IR, LP, MR, SR, IO [4,10] (Fig. 1). The midbrain lesion may have caused damage to one or a number of extraocular nerve fibre bundles. The midbrain was divided into anteromedial, lateral, and dorsal regions according to the arterial supply areas (Fig. 1), which are supplied by the superior medial midbrain branch, the lateral midbrain branch, and the dorsal midbrain branch, respectively, with the superior medial midbrain branch mainly emanating from the P1 segment of the posterior cerebral artery or the superior cerebellar artery, including the medial and lateral branches [18]. Infarcts in the anteromedial midbrain region are the most common type, and most patients present with impaired eye movement, mainly due to large-atherosclerotic and small-atherosclerotic types [2,11,12,16,19].

Table II. Clinical characteristics of patients with isolated MI-induced oculomotor paralysis (OP)

Variables	Isolated MI-induced OP (n = 33) n (%)
Damaged parts	
Midbrain	18 (54.5)
Brain	15 (45.5)
Damaged side	
Right	15 (45.5)
Left	9 (27.3)
Bilateral	9 (27.3)
Damaged brain regions in the midbrain	
Anterior medial area	23 (69.7)
Dorsal area	4 (12.1)
Anterior area	5 (15.2)
Dorsal medial area	1 (3.0)
Type of the ocular motor nerve palsy	
Up	10 (30.3)
Down	15 (45.5)
Adduction	25 (75.8)
Ptosis	9 (27.3)
Eyelid contracture	9 (27.3)
The affected oculomotor muscle	
SP	0 (0.0)
IR	11 (33.3)
LP	4 (12.1)
MR	25 (75.8)
SR	11 (33.3)
IO	8 (24.2)

SP – pupillary sphincter, IR – inferior rectus, LP – levator palpebrae, MR – medial rectus, SR – superior rectus, IO – inferior oblique

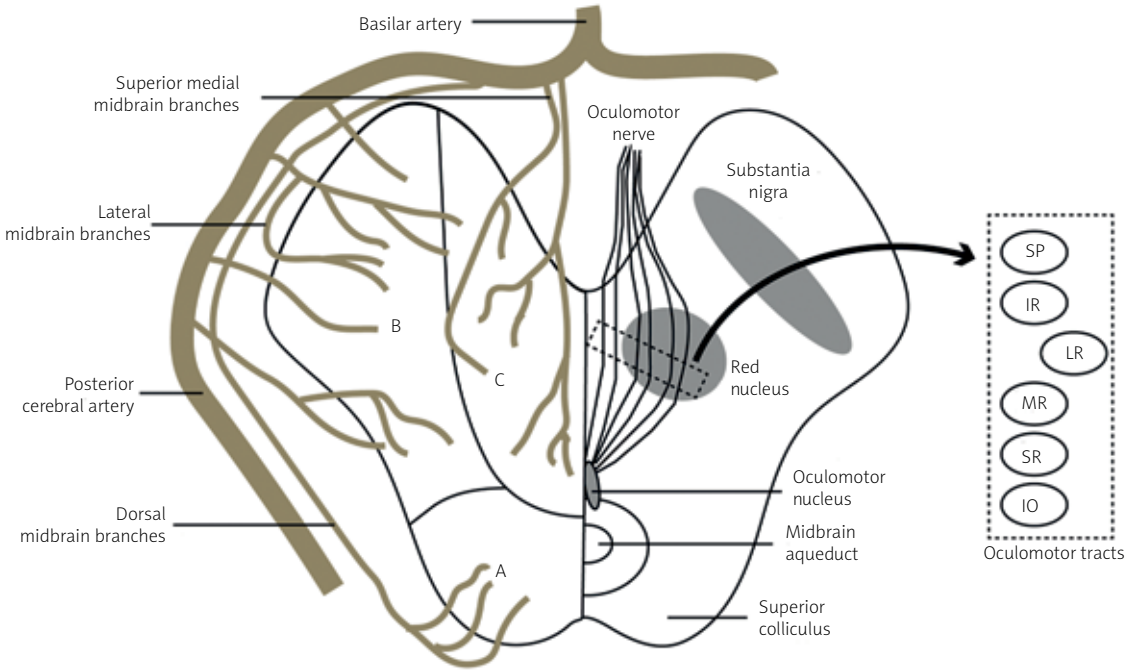

Fig. 1. Schematic diagram of the midbrain regions and arrangement of the oculomotor nerve bundle. The midbrain was divided into the dorsal region (**A**), lateral region (**B**), and anteromedial region (**C**) according to the arterial supply areas. The oculomotor nerve nucleus and the oculomotor nerve tracts are located in the anteromedial region, were provided by the superior medial midbrain branch. The oculomotor nerve tracts are arranged from the lateral side to the medial side in the following order: SP, IR, LP, MR, SR, IO. SP – pupillary sphincter, SR – superior rectus, LP – levator palpebrae, MR – medial rectus, IR – inferior rectus, IO – inferior oblique.

Of the 33 patients in the simple MI group, 24 had OP symptoms confined to unilateral eye, and all motor components and pupillary sphincter muscles of their contralateral eyes were unaffected, manifesting as different combinations of extraocular muscle paralysis. The involved extraocular muscles included MR, SR, IR, and LP. The lesion location shown by midbrain MRI involved the infarction of the anteromedial region of the midbrain, considered an acute midbrain infarction that should be associated with subnuclear root filament lesions, similar to previous reports [24]. Nine patients' OP symptoms involved bilateral eyes and all of them had bilateral elevation, adduction and depression palsy, and the lesion involved bilateral anteromedial region of midbrain infarction, and 1 patient with MR suggested the presence of acute lacunar infarction in the right thalamus and midbrain, which presented as slightly limited elevation, depression palsy of the left eye and limited elevation, adduction and depression palsy of the right eye, and the involved extraocular muscles included MR, SR, and IR. Compared with the nerve fibres innervating the intraocular muscles, the oculomotor nerve fibres innervating the extraocular muscles seem to be more prone to ischemic injury [2,11,19]. 25 of the above 33 patients showed MR dyskinesia, probably because the nerve fibres innervating MR are located in the centre of the oculomotor nerve fibres (Fig. 1), MR is particularly prone to infarction.

There are some limitations in this study. First, this is a single-centre study with a relatively small sample size. The results might be influenced by the potential selection bias despite the consecutive inclusion. Therefore, it is necessary to conduct further larger-scale, multicentre trial to verify the results. Second, we did not evaluate the actual association between symptoms and MRI imaging due to the cross-sectional design. Hence, longitudinal studies are warranted to exclude potential confounding factors in this issue.

Conclusions

In this study, we characterized the Chinese patients with OP caused by pure MI as a population presenting with rapidly progressive symptoms, and having multiple cerebrovascular risk factors and typical MRI signs. Further effort should be undertaken to investigate

a new technique for the differential diagnosis of this atypical midbrain syndrome.

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Disclosure

The authors report no conflict of interest.

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