Clinical Study

Cranial nerve palsies accompanying pituitary tumour

Sang Hyun Kim, Kyu Chang Lee, Sun Ho Kim *

Department of Neurosurgery, Yonsei University College of Medicine, Yonsei Brain Research Institute, 134 Sudaemoon Gu Shinchon Dong, Seoul, Republic of Korea

Received 27 March 2006; accepted 26 July 2006

Abstract

We reviewed 12 patients with pituitary tumour and cranial nerve palsy to analyse the clinical characteristics, the radiographic appearances, and the outcome after surgery. All patients had pathologically nonfunctioning macroadenomas with evidence of apoplexy. The third cranial nerve was the most frequently affected, followed by the sixth and fourth cranial nerves. Third cranial nerve palsy manifested as a symptom sequence comprising mydriasis, followed by limitation of gaze and ptosis. These symptoms recovered in reverse order of development. The time taken for recovery of cranial nerve palsy after surgery was significantly correlated with the length of time between the onset of symptoms and surgery. Pituitary apoplexy appears to be the primary cause of cranial nerve palsy with pituitary tumour. Early surgical intervention is most likely to bring about rapid recovery from cranial nerve dysfunction.

Keywords: Cranial nerve palsy; Pituitary tumour; Pituitary apoplexy

1. Introduction

Pituitary tumours comprise approximately 8–15% of all brain tumours. They can cause diverse clinical symptoms, generally pressure symptoms and endocrinological abnormalities.1 Cranial nerve dysfunction due to pituitary tumour has been previously described,2–5 and is thought to occur in 5–17% of pituitary tumour patients, generally manifesting as dysfunction of the third, fourth, fifth and sixth cranial nerves, which pass through the cavernous sinus.

In the present study, we describe the characteristics of cranial nerve palsy in pituitary tumour patients and analyse their clinical outcome, as well as their histopathological and radiological findings. We also aimed to determine the features that clinically differentiate these cranial nerve palsies from other diseases with similar symptoms. Furthermore, we analyzed the relationship between the clinical outcome and the interval between the onset of symptoms and treatment to determine the necessity for urgent treatment.

2. Patients and methods

In this retrospective study, age, sex, severity of cranial nerve symptoms and outcome, as well as details of the recovery from cranial nerve palsy, were analysed from the medical records. Of 508 patients who underwent transsphenoidal pituitary tumour resection between November 1995 and April 2005 at our hospital, 12 (2.4%) had cranial nerve dysfunction, and were thus selected for this study. Patients with cranial nerve dysfunction due to obvious cavernous sinus invasion, were excluded from the study. In all patients, MRI and a endocrinological testing were performed. Cerebral angiography was performed to distinguish cranial nerve palsy from posterior communicating artery (P-Com) aneurysm. Radiological and histopathological findings and surgical video records were also reviewed. The results were analysed by using the t-test.

3. Results

Cranial nerve palsy was detected in 12 of 508 patients who underwent transsphenoidal pituitary tumour resection (2.4%; 10 men, two women). The ages of the patients...
ranged from 26 to 76 years (mean age 56 years). Men had a higher incidence of symptoms than women. In all 12 patients, the tumours were nonfunctioning macroadenomas, and all patients had pituitary apoplexy.

The clinical symptoms of the 12 patients are shown in Table 1. For analysis, clinical symptoms were classified into two categories: cranial nerve palsies (CP) and other symptoms (OS). OS included headache, nausea, ocular pain, and a burning sensation. All patients had at least one OS prior to or almost concurrently with the development of cranial nerve palsy. In particular, sudden and persistent very severe headaches developed in all patients. The interval between the development of OS and surgery (OS duration) was 14.4 days on average.

Palsies of the third, fourth and sixth cranial nerves were included in the CP group. Three patients experienced palsies of two cranial nerves simultaneously. There were 10 patients with third cranial nerve palsy, four with sixth cranial nerve palsy, and one with fourth cranial nerve palsy. Of the 10 patients with third cranial nerve palsy, nine developed all three components, including mydriasis, limitation of gaze, and ptosis. The order of symptom development was identical in all patients: mydriasis developed first, followed by limitation of gaze, then ptosis. Only one patient developed mydriasis and limitation of gaze without ptosis. There was no misregeneration of the third nerve. After surgery, the symptoms of all patients improved in reverse order to that in which they developed. The average interval between the development of specific CP symptoms and surgery (CP duration) was 11.6 days.

Cranial nerve palsy caused by pituitary tumour and that caused by other diseases, particularly cerebral aneurysm in the P-Com artery, could not be differentiated on the basis of clinical symptoms alone.

MRI was done for all patients prior to surgery. Cystic degeneration, corresponding to an area of relatively strong intensity in the interior of the tumour, and findings suspicious of pituitary apoplexy were detected. This could be more readily and clearly detected on T2 coronal images (Figs. 1, and 2). With dynamic enhancement, lateral displacement or bowing of the medial wall of the cavernous sinus was observed, and absence of enhancement of the venous plexus of the cavernous sinus was also a prominent finding.

Tumor resection was performed using a transsphenoidal approach, and the tumour was completely resected for all patients. At surgery, evidence of haemorrhage within the tumour was detected in all patients, but direct invasion of the cavernous sinus wall was not detected in any patient. After surgery, all symptoms of cranial nerve palsy in all patients resolved. The interval between surgery and complete disappearance of the cranial nerve palsy was 31.8 days on average.

As shown in Table 1, the interval between the development of cranial nerve palsy and surgery (CP duration) and the interval between the development of other symptoms and surgery (OS duration) correlated inversely and significantly ($p < 0.05$) with the length of time required for the symptoms to disappear, thus indicating that recovery from cranial nerve palsy was much swifter in patients who underwent surgery soon after the development of symptoms. In patients who had more than two cranial nerve palsies simultaneously, the third cranial nerve palsy developed first and remained after the disappearance of the other cranial nerve symptoms. The recovery period for third cranial nerve palsy was long.

4. Discussion

The mechanisms of cranial nerve palsy and the causes of cranial nerve palsy in pituitary tumour patients have been discussed by various investigators. The causes include direct compression of the nerve by the tumour, transmission of the pressure on the cavernous sinus wall from tumour expansion, oedematous expansion due to haemorrhage in the tumour, ischaemic infarction of the tumour, and direct infiltration by the tumour. In addition, as shown in our study, pituitary apoplexy can provoke or aggravate cranial nerve palsy, either alone or via an interaction with other predisposing factors. Large or invasive adenomas without haemorrhage can also produce cranial nerve deficits; however, patients who exhibited cranial nerve dysfunction due to cavernous sinus invasion were excluded from this study.

In the present study, the size of the tumours varied greatly, ranging from 1.5 to 4.0 cm in diameter. The degree of lateral extension varied as well. This suggests that a sudden increase of pressure in the tumour, due to pituitary apoplexy and the accompanying vascular compromise, may mediate a much more significant or direct injury on a cranial nerve than the size or orientation of growth of the tumour itself.

In regard to cranial nerve palsy due to pituitary tumour, it has been reported that third cranial nerve palsy develops most frequently, followed by sixth, then fourth or fifth cranial nerve palsies in that order. When present, diplopia seems to be caused by either third or sixth cranial nerve palsy alone, or by paralysis of various nerves participating in the movement of the eye. Similar to previous findings, third cranial nerve palsy was frequently detected in this study, followed by sixth and fourth cranial nerve palsies. Fifth cranial nerve palsy was not detected in our study.

Because the third cranial nerve is located horizontally in the same plane as the pituitary gland, the pressure from lateral growth of a pituitary tumour to compress the cavernous sinus is relatively easily transmitted to the third cranial nerve. This results in compression of the third cranial nerve between the tumour and the interclinoide ligament, commonly resulting in the development of third cranial nerve palsy.
Patients with pituitary tumours causing third cranial nerve palsy without visual field defects have been reported.\(^3,13,14\) The prognosis of these patients has been shown to be better than patients with visual field defects.\(^8,9,13\) In the present study, however, we did not detect any significant difference in the recovery time of third cranial nerve palsy with or without visual field defects. Thus, we believe that visual field defects do not have any significant influence on prognosis. Furthermore, the average duration of recovery of patients with third cranial nerve palsy alone and patients with simultaneous third and sixth cranial nerve palsies was 36 days, with no statistically significant difference.

In the present study, the third cranial nerve was found to be involved first when more than one cranial nerve was involved, and this nerve took the longest time to recover. A possible explanation for this finding is that third cranial nerve palsy develops gradually as a result of tumours slowly growing laterally rather than above the sella turcica, compressing the cavernous sinus. Subsequently, pituitary apoplexy occurs, and the sudden impact on the third cranial nerve finally induces third cranial nerve palsy.\(^9\) Recovery is slow, due to the relatively low compliance of the third nerve to compression or stretching. Hence, third cranial nerve palsy may be the most important indicator of complete recovery after surgery.

Fourth cranial nerve palsy developed in association with paralysis of other nerves for movement of the eye, rather than in isolation. In such patients, panophthalmoplegia occurs, and such a pattern is a decisive indicator of pituitary apoplexy.\(^5\) The fifth cranial nerve can retain its function even when the nerve is extended to four times its original length.\(^9\) Development of fifth cranial nerve palsy implies actual infiltration of the tumour into the external wall of the cavernous sinus.\(^2\) It does not develop simply due to compression by the tumour. In patients with fifth cranial nerve palsy, erosion of the petrous bone has frequently been detected on X-rays. Such findings support the above description.\(^2,9,15\)

Sixth nerve palsy, although much less frequent, has also been reported. A proposed mechanism by which isolated sixth nerve palsy may occur is extension of the tumour backwards along Dorello’s canal, which contains the sixth cranial nerve along with the inferior petrosal sinus.\(^2,5\) Accordingly, in our patient with isolated sixth cranial nerve palsy, the tumour was found to have undergone posterior expansion, resulting in erosion of the surrounding basal bone.

In the present study, pituitary apoplexy was found histopathologically in all patients. Because pituitary apoplexy can present with variable MRI features, it is difficult to define its specific features. Nevertheless, it is important to understand the characteristics of each patient based on the MRI for early diagnosis and differentiation.\(^10\) In 11 patients analyzed in the present study, heterogeneous signal intensity in the intrasellar space was detected. In addition, high signal intensity was detected in the intrasellar area on T1-weighted images, with high-signal intensity clearly seen in the general vicinity also.\(^16\)

In the later part of the study period, T2-weighted images were added to our MRI protocol to differentiate

<table>
<thead>
<tr>
<th>No.</th>
<th>Age</th>
<th>Sex</th>
<th>Third CN</th>
<th>Fourth CN</th>
<th>Sixth CN</th>
<th>Duration of CNP (days)</th>
<th>Other symptoms (OS)</th>
<th>Duration of OS (days)</th>
<th>Time until full recovery (postoperative days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>62</td>
<td>M</td>
<td>Mydriasis, limitation of gaze, R ptosis</td>
<td>–</td>
<td>–</td>
<td>4</td>
<td>Severe headache, nausea</td>
<td>5</td>
<td>27</td>
</tr>
<tr>
<td>2</td>
<td>46</td>
<td>M</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>6</td>
<td>Headache, nausea</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>58</td>
<td>M</td>
<td>Mydriasis, limitation of gaze, R ptosis</td>
<td>–</td>
<td>–</td>
<td>5</td>
<td>Severe headache, nausea, fever</td>
<td>5</td>
<td>29</td>
</tr>
<tr>
<td>4</td>
<td>65</td>
<td>M</td>
<td>Mydriasis, limitation of gaze, L ptosis</td>
<td>–</td>
<td>+</td>
<td>13</td>
<td>Severe headache, ocular pain</td>
<td>12</td>
<td>37</td>
</tr>
<tr>
<td>5</td>
<td>56</td>
<td>M</td>
<td>Mydriasis, limitation of gaze</td>
<td>–</td>
<td>–</td>
<td>12</td>
<td>Severe headache</td>
<td>14</td>
<td>40</td>
</tr>
<tr>
<td>6</td>
<td>54</td>
<td>F</td>
<td>Mydriasis, limitation of gaze, L ptosis</td>
<td>–</td>
<td>–</td>
<td>9</td>
<td>Severe headache, nausea</td>
<td>12</td>
<td>28</td>
</tr>
<tr>
<td>7</td>
<td>26</td>
<td>M</td>
<td>Mydriasis, limitation of gaze, R ptosis</td>
<td>–</td>
<td>–</td>
<td>9</td>
<td>Severe headache</td>
<td>11</td>
<td>25</td>
</tr>
<tr>
<td>8</td>
<td>44</td>
<td>M</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>10</td>
<td>Severe headache</td>
<td>15</td>
<td>19</td>
</tr>
<tr>
<td>9</td>
<td>68</td>
<td>M</td>
<td>Mydriasis, limitation of gaze, R ptosis</td>
<td>–</td>
<td>–</td>
<td>48</td>
<td>Severe headache, nausea</td>
<td>49</td>
<td>73</td>
</tr>
<tr>
<td>10</td>
<td>46</td>
<td>F</td>
<td>Mydriasis, limitation of gaze, L ptosis</td>
<td>–</td>
<td>–</td>
<td>6</td>
<td>Severe headache, nausea</td>
<td>9</td>
<td>21</td>
</tr>
<tr>
<td>11</td>
<td>71</td>
<td>M</td>
<td>Mydriasis, limitation of gaze, R ptosis</td>
<td>–</td>
<td>+</td>
<td>15</td>
<td>Dull headache</td>
<td>15</td>
<td>49</td>
</tr>
<tr>
<td>12</td>
<td>71</td>
<td>M</td>
<td>Mydriasis, limitation of gaze, R ptosis</td>
<td>–</td>
<td>+</td>
<td>9</td>
<td>Severe headache</td>
<td>17</td>
<td>31</td>
</tr>
</tbody>
</table>

CN, cranial nerve; R, right; L, left.

Table 1
Clinical features of patients with cranial nerve palsy (CNP) and pituitary tumour
haemorrhage from other tumours originating from the pituitary gland. It should be noted that T2-weighted imaging plays a role not only in making a diagnosis in the early stages of haemorrhage, infarction, oedema, and lesions detected during apoplexy, but also in allowing more detailed anatomical observation. In addition, the formation of a fluid-fluid level by haemorrhage in a pituitary tumour, as well as the time of haemorrhage can be predicted. Contrast-enhanced images do not provide additional information for diagnosis. Therefore, T2-weighted images from patients with suspected pituitary apoplexy are important for early differential diagnosis.

Although patients with invasion of the cavernous sinus were excluded from this study, the presence or absence of invasion of the cavernous sinus is not only important for surgical planning, but also a factor that greatly influences...
the outcome of surgery. Thus, assessment of invasion of the cavernous sinus prior to surgery is very important. However, in the present study, in which MRI occurred prior to surgery, we could not provide a sufficiently clear standard for assessment of invasion of the cavernous sinus: loss or poor resolution of the medial wall of the cavernous sinus was seen in all patients. Although effacement with the cranial nerves was not always visible, we found stagnated blood flow in the cavernous venous plexus on T1-weighted dynamic images. This may be valuable in predicting the difficulty of surgery and prognosis.

In all patients, clinical symptoms such as headache and nausea occurred concurrently with or as early as 5 days before the onset of cranial nerve palsy. However, development of cranial nerve palsy prior to OS did not occur. Hence, it is highly likely that the OS appear at the time of a haemorrhagic event inside a tumour, and that cranial nerve palsy develops when the cranial nerve exceeds its level of tolerance due to the effect of the increased pressure in the tumour and accompanying oedema.

In the present study, the time to recovery from cranial nerve palsy after surgery and the interval between the development of symptoms and surgery were positively and significantly correlated. The interval between the appearance of symptoms and surgery may be considered an important factor for recovery after surgery. This result suggests that cranial nerve palsy due to pituitary tumour can be treated with a high rate of success if the surgery is performed as early as possible after diagnosis.

Pituitary apoplexy and subarachnoid haemorrhage show similar symptoms, including sudden headache, neck stiffness, and change in consciousness. In addition, cerebral aneurysm and pituitary apoplexy together are found in 7.4% of all pituitary tumour patients. In such cases, it is difficult to differentiate cerebral aneurysm from pituitary apoplexy on the basis of clinical symptoms alone. Therefore, cerebral angiography or magnetic resonance angiography (MRA) is required. We attempted to differentiate between third cranial nerve palsy caused by a pituitary tumour and cerebral aneurysm occurring on the P-Com by analyzing the clinical symptoms of patients.

Lee et al. found third cranial nerve palsy as an early symptom in 38% of patients with P-Com aneurysm. The visceral element of the third cranial nerve controls constriction of the palpebral fissure and runs close to the surface of the nerve. Therefore, third cranial nerve palsy with ptosis can easily develop in response to simple pressure on the nerve. The change in pupil size is controlled by parasympathetic nerves, and thus may be less affected than eye movement. Although we speculate that these two diseases can be differentiated clinically because of their lesion- al anatomy; the site compressing the third cranial nerve and the different mechanisms involved in symptom development are difficult to characterize on the basis of clinical symptoms alone given that the order of the appearance of clinical symptoms and the pattern of symptoms were not significantly different. Therefore, it is necessary to perform preoperative cerebral angiography or MRA for differentiation of these two diseases.

5. Conclusions

All patients in the present study had nonfunctioning macroadenomas, with evidence of pituitary apoplexy. Cranial nerve palsy occurred in the third, sixth, and fourth nerves (in that order of frequency). Symptoms developed in the order of mydriasis, limitation of gaze, and then ptosis in patients with third cranial nerve palsy, and recovery from symptoms was in reverse order. A shorter interval between the onset of cranial nerve palsy and surgery correlated with a more expedient recovery. These results suggest that early recovery from cranial nerve palsy, without neurologic deficits, can be expected if the surgery is performed as early as possible after a prompt diagnosis.

References