Clinical Features and Treatment of Spinal Myxopapillary Ependymoma: A Series of 15 Cases

Jie Li*1, Shi-Ting Li*2, Ming-Jie Zhu3, Yong-Min Li1, Xu Wang1, Yu-Jun Li1, Bin Li2, Xiao-Qiang Wang2

*These Authors Contributed Equally to this Work

1Department of Spine, Second Hospital of Tangshan, Tangshan, China 2Department of Neurosurgery, Xinhua Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China 3Department of Pathology, Xinhua Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China

Summary

Background: Myxopapillary ependymoma is a rare ependymoma arising almost exclusively from the filum terminale. Spinal myxopapillary ependymoma (SME) is even rarer. However, up to now there has been no ideal treatment for SME.

Methods: The patients received surgical removal from January 2000 to December 2009. Clinical presentation, diagnosis, treatment, therapeutic outcome and follow-up results of 15 patients, who were pathologically diagnosed with SME, were retrospectively studied.

Results: The patients included eleven males and four females, with an age range of 13 to 57 years (mean 36.5 years). The length of follow-up was determined from the date of surgery to the patient's most recent clinic visit. Histological examinations showed WHO grade I myxopapillary ependymomas. Gross total removal was achieved in seven patients, piecemeal total removal in two patients, and subtotal removal in six patients. Eight patients were neurologically preserved with Frankel Grade E one year later. Three patients who had recurrence of the tumor for this operation had no improvement after the subtotal resection. There was no tumor recurrence during the follow-up. There was no death in this group.

Conclusions: The onset of SME is not characteristic, so pristine diagnosis is very important. Surgery is the routine treatment for SME; gross total removal has better outcomes than piecemeal total removal and subtotal removal. Subtotal removal is achieved in the patients who have the recurrence before this operation. They have no improvement until the recent follow-up. This study provides some directions for further research and treatment of SME.

Key words: Myxopapillary ependymoma; spine; surgery; prognosis

Spinal Miksopapiller Ependimomların Klinik Özellikleri ve Tedavisi: 15 Olguluk Klinik Seri

Özet


Anahtar Kelimeler: Mikropapiller ependimom; spinal kord; cerrahi; prognoz

INTRODUCTION
Myxopapillary ependymoma is an ependymoma arising almost exclusively from the filum terminale. There have been some reports of this kind of ependymoma till now; however, most of the reported myxopapillary ependymoma cases have been individual or small case reports. Ependymoma of the spinal cord accounts for nearly 90% of primary tumors in the cauda equina region and makes up 40%-50% of all spinal ependymomas in the adults and 8% to 14% of all spinal ependymomas in children younger than 16 years. Myxopapillary ependymoma was firstly reported by Kernohan as a subtype of ependymoma in 1932, it is a grade I ependymoma according to the WHO classification and is considered to have a good prognosis. Most of them grow slowly, and have smooth circumscription by a connective tissue capsule and lack of firm attachment to or incorporation of surrounding spinal nerve root. Despite of its benign nature, some patients who received subtotal tumor removal had a relative poor prognosis. SME can cause typical symptoms such as radicular and back pain, which is more pronounced at night and in recumbent position. In addition, motor, sensory, urinary, and gait abnormalities may also develop. However, patients frequently have a long history of nonspecific complaints prior to clinical presentation because of the slow growth and well-circumscribed nature of these diseases. So the pristine diagnosis and treatment become very important. However, there is still not a standard therapeutic principle for this disease up to now. Radiotherapy and chemotherapy after operation are still controversial. This study is to retrospectively review the surgical results of SME patients and to analyze the diagnosis, outcome and surgical strategy of this disease. And this study can give some suggestions or directions about further research of SME.

MATERIAL AND METHODS
From January 2000 to December 2009, fifteen patients underwent surgery for SME. No patient was lost in the follow-up. Of the fifteen patients, eleven were males and four were females, with an age range of 13-57 years old (mean 36.5 years). The demographic data, clinical presentation, radiographic presentation, distribution, histopathology analysis, treatment method and outcome of the fifteen patients were retrospectively reviewed. The length of follow-up was determined from the date of surgery to the patient's most recent visit. All patients underwent MR or enhanced MR before and after operation, and were diagnosed with myxopapillary ependymoma (WHO grade I)
pathologically. Tissue specimens were fixed in 10% buffered formaldehyde solution, embedded in paraffin wax, and stained using hematoxylin-eosin according to standard protocol. Sections were cut to 3 μm thick. Immunohistochemical stains were performed using standard reagents and Envision techniques. The following antibodies were used for immunohistochemistry: antibodies against vimentin (1:100), glial fibrillary acidic protein (GFAP)(1:100), S-100 (1:300). All antibodies were obtained from M/S Dako Patts, Denmark.

RESULTS

Clinical presentation

The clinical data of the fifteen SME patients were as in Table 1. Three patients had operation for recurrent tumor and twelve had no operation history. The duration of symptoms before diagnoses ranged from two months to ten years, with an average of 28.7 months. Neurologic function was evaluated by Frankel classification (A = complete motor and sensory loss, B = preserved sensation only, C = motor and sensory incomplete function, D = useful motor function, and E = no motor or sensory function disorder). Low back and hip pain were the main complaints. The pain radiated to the extremities and aggregated at night. Two patients (13%) were pain free, nine (60%) had moderate pain and four (27%) had severe pain. Sensory disturbances were documented in seven (47%) patients; the location of deficits varied with the tumor site. Two patients had hypoesthesia of the lower extremities. Three patients had hypalgesia and hypesthesia of the left lower extremity. And one patient had hypesthesia of the shanks. Other symptoms included limb weakness in eight patients (53%) and bowel or bladder dysfunction in nine patients (60%).

Table 1. Clinical data of 15 patients with spinal myxopapillary ependymoma

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age/sex</th>
<th>Tumor location</th>
<th>Previous resection</th>
<th>Resection</th>
<th>Neurological function (Frankel grade)</th>
</tr>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pre-op</td>
<td>Post-op 1-mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>F/U</td>
<td>F/U</td>
</tr>
<tr>
<td>1</td>
<td>14/M</td>
<td>T11-L1</td>
<td>No</td>
<td>Total</td>
<td>D</td>
</tr>
<tr>
<td>2</td>
<td>57/M</td>
<td>T11-L1</td>
<td>Yes</td>
<td>Subtotal</td>
<td>C</td>
</tr>
<tr>
<td>3</td>
<td>18/M</td>
<td>L4-S2</td>
<td>No</td>
<td>Subtotal</td>
<td>C</td>
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<tr>
<td>4</td>
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<td>L3-S1</td>
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<td>E</td>
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<tr>
<td>5</td>
<td>13/M</td>
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<td>Total</td>
<td>E</td>
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<tr>
<td>6</td>
<td>28/F</td>
<td>L2-L3</td>
<td>No</td>
<td>Total</td>
<td>D</td>
</tr>
<tr>
<td>7</td>
<td>49/M</td>
<td>T12-L3</td>
<td>Yes</td>
<td>Subtotal</td>
<td>D</td>
</tr>
<tr>
<td>8</td>
<td>46/M</td>
<td>L2-L3</td>
<td>No</td>
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<td>E</td>
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<tr>
<td>9</td>
<td>55/F</td>
<td>L2-S2</td>
<td>Yes</td>
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<tr>
<td>10</td>
<td>42/F</td>
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<tr>
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<td>26/M</td>
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<td>Total</td>
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<tr>
<td>12</td>
<td>47/M</td>
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<td>No</td>
<td>Subtotal</td>
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<tr>
<td>13</td>
<td>39/M</td>
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<td>No</td>
<td>Total</td>
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<tr>
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<td>L1-S2</td>
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<td>D</td>
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<td>31/F</td>
<td>L2-L3</td>
<td>No</td>
<td>Total</td>
<td>E</td>
</tr>
</tbody>
</table>

Abbreviation: F: female; F/U: follow-up; mo: month; M: male; post-op: post-operation; pre-op: pre-operation; Yr: year.
**Radiographic presentation**

All patients underwent MRI or enhanced MRI before the operation. MRI findings showed that all the masses were adjacent to the conus region. The involved spinal segments ranged from two to seven segments (median 3.5 vertebrae). In the axial view, six cases had the tumors in the central part of the thecal sac, four cases in the marginal portion, and five cases all over the thecal sac. On T1-weighted image, the masses appeared isointense relative to the spinal cord. On T2-weighted image, the mass showed homogeneous hyperintensity in eleven cases and inhomogeneous signal intensity in four cases (Figs. 1-2).

**Distribution**

Totally 53 vertebrae were affected in the fifteen patients. Five patients had the tumors involving two spinal segments, two patients involving three spinal segments, six patients involving four spinal segments, one patient involving six spinal segments, and one patient involving seven spinal segments. The thoracolumbar spine was involved in five cases, the lumbar spine was involved in five cases, and the lumbo-sacral spine was involved in five cases.

**Pathology**

All patients received intraoperative examination of frozen section margin. The histopathologic diagnoses were myxopapillary ependymoma, a grade I ependymoma according to WHO classification. It was noteworthy for pseudo-papillary architecture, arborizing vasculature, and mucin production. The lesion was characterized by cuboidal tumor cells, with GFAP expression and lack of cytokeratin expression, and with surrounding blood vessels in a mucoid matrix. Mitotic activity was very low or absent. All the fifteen surgical specimens had routine hematoxylin-eosin-stained. The tumor presented papillae with abundant area of myxoid stroma containing capillary blood vessels, and perivascular pseudo-rosette was seen in the tumor tissue. Immunohistochemical stains showed ten lesions were positive for vimentin and S-100 antigen respectively, whereas all the fifteen lesions were positive for GFAP.

![Fig 1: MRI of SME (T11-L1), isointense on sagittal T1-weighted imaging.](image1)

![Fig 2: MRI of SME (T11-L1), hyperintense on sagittal T2-weighted imaging.](image2)
Surgical treatment

Surgical resection was the routine treatment for SME patients. The extents of surgery were determined by the clinical presentation and preoperative imaging studies. Gross total removal was achieved in seven patients (47%), piecemeal total removal in two patients (13%) and subtotal removal in six patients (40%). Gross total removal was the first choice during the surgery; it not only reduced the potential for tumor spillage but also avoided bleeding from the tumor during dissection. Sometimes very large tumors may hinder the visualization of the dissection planes; so internal debulking such as piecemeal total removal could be performed to decrease the amount of traction on the cord. Subtotal resection was adopted due to the nerve root and conus involvement and unencapsulated tumor. In our studies, three patients experienced local recurrence and underwent subtotal removal. In the encapsulated tumors, total removal could be accomplished and there was no residual disease on postoperative imaging scan. But for the unencapsulated tumors, especially the recurrent tumors, total removal could not be achieved, and subtotal removal became the first choice. No patients received postoperative radiotherapy or chemotherapy in our group.

Clinical follow-up

Postoperative follow-up was from 7 months to 6 years (mean 2.5 years), and no patient was lost to follow-up. After operation, four patients had improvement, one had bladder dysfunction and ten kept the Frankel Grade, but with the pain relieved to various degrees. Six months after operation, case 2 felt that the pain of the low back and extremity became more serious than before. However, he refused to further examination and demanded further observation. The remaining patients had no recurrence. At the last follow-up, seven patients were asymptomatic, returned to normal life, and sought employment; four patients were Frankel Grade E but had moderate pain; and four patients had persistent neurological deficits. No patient died at the last follow-up.

Illustrative cases

Case 1

The 14-year-old boy presented reported progressive weakness and numb of the left leg for 4.5 months. He also had bowel and bladder dysfunctions. He underwent a

Fig 3: Histologic examination of SME The lesion was characterized by cuboidal tumor cells, with surrounding blood vessels in a mucoid matrix. (H-E, original magnification ×200).
Case 1

Thoracolumbar MR imaging examination which showed an intramedullary lesion at T11-L1 level. The patient underwent surgery for a gross total removal. Postoperative MR imaging showed a total removal. No radiotherapy was given after operation. The postoperative clinical status was improved, with the strength and sensation reaching normal level. He still had bowel and bladder dysfunction during the follow-up.

**Case 2**

The 57-year-old man reported progressive weakness and numb of the lower extremity, low back pain and bowel and bladder dysfunction for two years. He received operation for the same disease ten years ago. The muscle strength of the lower extremity was grade III. Thoracolumbar MR imaging showed an intramedullary lesion at T11-L2 level. The patient underwent subtotal removal due to the nerve root and conus involvement and unencapsulated tumor. No radiotherapy was given after operation. In the early postoperative period, the patient reported an abatement of the low back pain, and the pain became serious after our later follow-up. Until now he could not walk and took analgesic drug for pain release. There was no noticeable improvement of bowel and bladder function after operation. He received no enhanced MRI during the follow-up.

**DISCUSSION**

**Clinical manifestation and radiographic finding**

Myxopapillary ependymoma makes up 40%-50% of all spinal ependymomas in the adults and 8%-14% of all spinal ependymomas in children. Most of the patients in our study had a non-specific presentation. The most common complaint was pain, which was often pronounced in the low back and hip, especially at nighttime. Other common symptoms included sciatica, weakness of lower extremities, loss of sensation, and bladder and bowel dysfunction. Sometimes the spinal claudication could also be seen.

MRI was helpful in identifying the extent of the tumor and its relationship with intraspinal structures. The MRI features of SME included: (1) an intradural extramedullary thoracolumbar mass, (2) the tumor extends for several vertebral levels in lumbar and sacral canal, (3) it was hypointense to isointense on T1-weighted images, (4) hyperintense on T2 weighted images, (5) intense, homogeneous enhancement after IV administration of contrast, (6) a region of slight lower intensity at tumor margin on T2-weighted sequences, and (7) cystic rostral or caudal degeneration exists. MRI was also need to make sure whether there was any recurrence or remainder after operation.

**Diagnosis and differential diagnosis**

The clinical and radiographic findings of intramedullary lesions are not specific enough to identify the disease. Diagnosis of SME depends on a combination of clinical, radiographic and pathological findings. The key point of diagnosis is the pathological result. Myxopapillary ependymoma had specific morphologic features. The gross appearance of the encapsulated myxopapillary ependymoma, although nonspecific, was characteristic. A delicate fibrous capsule representing the stroma of the filum terminale invested the ovoid to sausage-shaped vascular tumors that were situated within, and often limited to the filum. Direct proximal extension with incorporation of the conus medullaris was not uncommon. The capsular surfaces of the tumor varied from smooth to nodular, occasionally rendering assessment of total encapsulation difficult. Unencapsulated tumors assumed the form of vascular multinodular implants involving the spinal cord, nerve roots, and meninges. The dominant microscopic architectural feature of tumors were pseudopapillae formation associated, to a variable extent, with symmetrical zones of
mucoid matrix surrounding branching tumescent vessels, as well as accumulation of mucin within and between tumor cells. Immunostaining for dial fibrillary acidic protein were strongly positive in fibrillated ependymal cells, but cuboidal and columnar epithelial forms were less reactive. Neurofilament protein immunostaining were uniformly negative, whereas cytoplasmic S-100 immunoreactivity was unpredictable, patchy in distribution, and variable in intensity.\(^{(12)}\)

Patients with myxopapillary ependymoma had a non-specific presentation. And the spinal claudication could also be one of the symptoms of myxopapillary ependymomas.\(^{(22)}\) The symptoms consisted of pain that occurs on walking, usually in the calves, which is rapidly relieved by stooping, sitting or otherwise adopting a flexed posture of the hips, and recurs on attempting to walk again. These symptoms may mimic some disc diseases such as lumbar disc herniation and lumbar spinal stenosis. Other intradural extramedullary lesions in the region of the conus medullaris include paragangliomas, nerve sheath tumors, neurofibromas, meningiomas, and metastases. Less frequently observed tumors include hemangioblastomas, lipomas, and dermoid and epidermoid tumors.\(^{(13)}\) Other rare tumors have been reported. Consequently, if a patient presents with the combination of a long prodrome and nonspecific lower extremity symptoms, along with the discovery during imaging of a large tumor in the cauda equina region, then the suspicion that the mass is a myxopapillary ependymoma is high. And further verification can be obtained from the pathological results.

**Treatment and follow-up**

Myxopapillary ependymoma is a benign tumor with slow growth. Up to now, no uniform principles for clinical treatment and the standard criteria for the scientific assessment of various treatments have been reported. Based on the benign character of myxopapillary ependymoma, surgery became the first choice for treatment. The surgical methods included gross total removal, piecemeal total removal and subtotal removal. Favorable features permitting gross total removal included smooth circumscription by a capsule, limitation to the filum terminale, preventing firm incorporation of surrounding structures, such as nerve root or conus. The grossly encapsulated tumors could be removed intactly, and the prognosis was excellent especially for smaller lesions in which complete removal was considered curative. Seven patients in our group received gross total removal; two patients were Frankel Grade D before operation, and reached Frankel Grade E after the tumor resection, and five patients were Frankel Grade E before operation, and kept Frankel Grade E during our follow-up, and there was no recurrence.

If the tumor was large or unencapsulated, or infiltrated and adhered to the nerve roots of cauda equina and/or conus medullaris, the piecemeal total removal could be adopted. Tumor separation and manipulation of the surrounding neural tissue may cause neurologic injury or capsule rupture. The reasons of capsule rupture in myxopapillary ependymoma were not clear, but in spinal cord ependymoma, trauma was known to cause hemorrhage, tumor rupture, and dissemination along the nerve root.\(^{(16)}\) Intratumoral hemorrhage may cause tumor rupture and seeding along the surrounding nerve roots. No matter how the meticulous detachment of tumor was performed, nerve root and/or conus may be embedded in the tumor tissue, and manipulation of the nerve may cause irreversible neurologic injury. In our study, two patients received piecemeal total removal; one patient was Frankel Grade D before operation, and reached to Frankel Grade E after the tumor resection; and another was Frankel Grade D before operation, but developed bladder dysfunction after the tumor removal. And
the dysfunction had not been improved until the recent follow-up. Celli et al compared the surgical outcomes between tumors confined to the filum terminale and those infiltrating or adhering to the nervous tissue. They found confinement of tumor to the filum terminale and total tumor removal led to better prognosis. Neurologic deterioration after surgery was seen only in infiltrating tumor group because of tumor recurrence as a long-term result. There were no clinical reports regarding postoperative neurologic deficit caused by piecemeal removal of unencapsulated myxopapillary ependymoma of the cauda equina region. But in our study, the patient who received piecemeal total removal also developed bladder dysfunction, which not recovered after the operation, which may due to the manipulation during the operation. The removal of the lesion perhaps injured the cauda equina region, which led to bladder and bowel dysfunction.

Six patients in our group received the subtotal removal, including three received operation before, with the first operation being subtotal or piecemeal removal. None of the three patients had any improvement after the first operation. Two patients kept Frankel Grade D and one patient kept Frankel Grade C. All of the three patients still remained the same Frankel Grade until the recent follow-up. The patient who kept Frankel Grade C developed serious pain and could not walk until the latest follow-up; he took analgesic drug for pain release. Fortunately, no more recurrence was found among these patients, and all of them were alive.

During our study, no patient received radiotherapy after operation. Most articles had described the propriety of postoperative radiation and the tumor recurrence. The recurrence rate of myxopapillary ependymoma after surgery varied with treatments. Postoperative radiation therapy had been advocated as an adjunctive treatment for controlling spinal ependymoma. However, the effect of irradiation after the removal was controversial. Akyurek et al. noted that regardless of the extent of resection, adjuvant radiotherapy significantly reduced the rate of tumor progression in 35 cases of myxopapillary ependymoma. But in a review of 131 cases, Ross and Rubinstein found no difference between patients who had undergone radiotherapy and those who had not, after total or subtotal resection. Difficulty to conduct prospective studies or controlled trials to determine the indications of adjunctive treatment had not given inclusive recommendation for postoperative radiotherapy. In our research, the histological finding in all patients was MPE (WHO grade I). Its mitotic activity was very low or absent. The possibility of recurrence was lower than high grade tumors. But for the patient who received the second operation, postoperative radiotherapy was necessary. There were some residual tumor parts, so the radiotherapy could resist further spread and reduce the rate of recurrence. However, there was no radiotherapy in our treatment. And no recurrence was found until the latest follow-up. We think that postoperative radiotherapy may not be necessary because the resection could be thorough after gross total removal. As for the patients who received the piecemeal total removal, postoperative radiotherapy was still suggested to reduce the recurrence rate. For the patients who had the recurrent tumor, radiotherapy after operation was thought to be necessary.

**Prognosis**

Myxopapillary ependymomas are benign lesions, whose prognosis is associated with the degrees of the operation. Sonneland et al found that completeness of tumor resection was the major factor for the likelihood of postoperative recurrence. Nakamura et al. found that, even after complete resection, if the capsule was violated, recurrence could occur.
gross total removal is better than piecemeal total removal and subtotal removal. Gross total removal can reduce the incidence of violating capsules during the manipulation. In our fifteen patients, seven attained gross total removal, two attained piecemeal total removal and six attained subtotal removal. No radiotherapy was given after operation. Fortunately, no recurrence has been found until the latest follow-up, and all patients are alive. The patients who received gross total removal have greater improvement than the patients who received piecemeal total removal or subtotal removal. Three patients received subtotal removal for tumor recurrence, but they have showed no improvement till now.

CONCLUSION
The onset of SME is not characteristic, so its diagnosis depends on a combination of clinical, radiographic and pathological findings. Although the optimal management of this tumor is still controversial, the routine treatment is surgery. The gross total removal has a better clinical outcome than piecemeal total removal and subtotal removal. Patients receiving gross total removal have obvious improvement after operation. For patients with recurrent tumors, subtotal removal should be performed and the tumor could not be removed completely, so these patients have a relatively poor prognosis. No radiotherapy was given in our patients, and no recurrence has been found until the latest follow-up. At present, the curative effect of radiotherapy and chemotherapy still needs to be further studied. Closer clinical follow-up and well-designed prospective studies are warranted in the future about SME.

Acknowledgements
We thank professor Jian-Kang Shen for expert opinions during the development of this manuscript. We also thank Ya-Xuan Wang for her collecting data. This work is supported by grants from China Postdoctoral Science Foundation (No. 20100480568). The authors report no conflict of interest concerning the materials used in this study or the findings specified in this paper.

Correspondence to:
Xiao-qiang Wang
E-mail: wangxq10@126.com

Received by: 25 October 2012
Revised by: 16 November 2012
Accepted: 21 November 2012

The Online Journal of Neurological Sciences (Turkish) 1984-2012
This e-journal is run by Ege University Faculty of Medicine, Dept. of Neurological Surgery, Bornova, Izmir-35100TR
as part of the Ege Neurological Surgery World Wide Web service.
Comments and feedback:
E-mail: editor@jns.dergisi.org
URL: http://www.jns.dergisi.org
Journal of Neurological Sciences (Turkish)
Abbr: J. Neurol. Sci.[Turk]
ISSN e1302-1664

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