Neurohypophyseal germinoma

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Of 16 patients the average age at treatment was 15.5 years (rouge 6-26) [1].

Diagnosis

Neurohypophyseal intracranial germinomas are rare neoplasms, with slow growth and variable clinical presentation that occasionally complicate their diagnosis in the early stages of the disease.

CSF-human chorionic gonadotropin (hCG) concentrations that exceed the established reference interval (undetectable values to 0.7 IU/L) in the presence of suprasellar lesions and pituitary stalk thickening must be considered pathological, establishing the need to exclude the presence of germinoma [2].

Although the determination of human chorionic gonadotropin (hCG) in serum and cerebrospinal fluid (CSF) may help, definitive diagnosis of these tumors is determined by the histopathological findings [3].

Although neurohypophyseal germinoma is known be a common initial symptom in cases of diabetes insipidus (DI), its radiological detection may take months or years even by a high-resolution magnetic resonance (MR) imaging. The term “occult neurohypophyseal germinoma” denotes such cases [4].

MR and CT

MR and CT images of 13 consecutive patients (seven males, six females; mean age: 15 years; range: 6-31 years) with neurohypophyseal germinoma were retrospectively analyzed. The diagnosis had been made either histologically (n=8) or clinically according to established criteria (n=5). All patients had been examined using MR imaging and CT before treatment.

On MR imaging, infundibular thickening (up to 16 mm) was observed in all 13 cases. Hyperintensity of the posterior pituitary on T1-weighted image was absent in all 13 cases (100%) and 12 of the 13 displayed central diabetes insipidus. Ten germinomas (77%) were isointense to cerebral cortex on T1-weighted image, but variable intensities were exhibited on T2-weighted image. MR images revealed intratumoral cysts in six cases (46%), most of which demonstrated intra-third ventricular extension. Eleven of the 13 cases (85%) revealed hyperdense solid components on unenhanced CT. Calcification was absent in all cases (100%).

Infundibular thickening, absence of the posterior pituitary high signal on T1-weighted image, lack of calcification and hyperdensity on unenhanced CT are common imaging features of neurohypophyseal germinoma [5].

Gallium-67 scintigraphy

67Ga studies in five male patients with histologically verified intracranial pure germinomas were evaluated. Two germinomas were located in the neurohypophysis, two in the pineal region, and one in both the neurohypophysis and pineal region. The control group included 36 patients with histologically verified pituitary macro-adenomas. 67Ga study at the time of original diagnosis showed an abnormal accumulation in two neurohypophyseal germinomas, and negative accumulation in the other germinomas. In the two patients with neurohypophyseal germinomas, 67Ga study showed an abnormal accumulation in the intracranial tumour region in accordance with magnetic resonance (MR) findings. After postoperative irradiation or chemoradiotherapy, MR imaging and 67Ga studies revealed the complete disappearance of this tumour and no metastatic spread. In one of these two patients, a whole-body 67Ga study demonstrated multiple bone metastases one year later, and the reduction of these metastatic regions after chemotherapy. 67Ga study disclosed negative accumulation in all 36 pituitary macroadenomas. Although 67Ga uptake by neurohypophyseal germinomas may not be specific for this condition, this approach may provide some clues for diagnosing patients with neurohypophyseal germinomas [6)].

Case series

2001

Long-term posttreatment Karnofsky Performance Score (KPS) and neurological status of 16 patients with neurohypophyseal (NH) germinomas were retrospectively analysed, in order to deduce the best treatment modality to achieve a good outcome. The average age at treatment was 15.5 years (rouge 6-26) and they were followed up for 107.3 months (26-209). The KPS averaged 81.5 (0-100). Three patients were below 60 in the KPS. The first one had hemiparesis due to a delayed cerebrovascular accident (CVA), and the second became indifferent and inactive with recent memory loss. The third died from marginal recurrence of tumour and subsequent systemic metastasis. The low scores were all more or less attributable to complications related to irradiation: delayed CVA, diffuse cortical atrophy and inappropriate selection of irradiation field, respectively. The second case had the tumour origin at the hypothalamus, which indicates intraparenchymal tumour location as another factor to worsen the quality of life (QOL). Visual field and acuity, and EOM impairment were observed in eight and five patients, respectively. It improved in all patients but one. The visual and EOM dysfunction recovered satisfactorily and was not a disabling factor. The intraparenchymal lesion resulting in hemiparesis and higher cortical dysfunction due to either irradiation-related complications or tumour invasion is a major determining factor of lower KPS. Irradiation related complications are considered to be avoidable by reducing radiation dosage with appropriate chemotherapy and/or proper selection of irradiation field. Patients with smaller tumour size of less than 20 mm had higher KPS. Accordingly, repeated studies of tumour markers and neuroimages are required in patients with idiopathic diabetes insipidis, in order to detect the tumour, if present, at the small-sized and early stage [7)].

2000

Eleven patients with neurohypophyseal GCTs underwent dynamic MR studies with Tl-weighted spin-echo (SE) or turbo SE techniques. Other infundibular lesions, including adenohypophysitis (n=3), Langerhans' cell histiocytosis (LCH, n=2), and 1 hemangioblastoma from von Hippel-Lindau disease,

were also evaluated. Serial images were obtained every 15 s (turbo SE) or 30 s (SE technique) for 240 s after rapid injection of contrast medium. The dynamic patterns were analyzed quantitatively with the contrast medium enhancement ratio.

On dynamic MR images, GCTs typically showed a gradual enhancement increase with a peak between 105 s and 180 s, while two showed a relatively rapid increase. LCH and hemangioblastoma showed a dynamic pattern similar to GCTs, while adenohypophysitis demonstrated a sharp rise and a steeper wash-out with an obvious peak before 90 s.

Typical dynamic pattern of GCTs was the gradual enhancement increase without wash-out. Dynamic MR imaging can distinguish GCTs from adenohypophysitis, but is not useful for differentiation from LCH [8)].

Sixteen patients (7 men and 9 women), aged 6 to 26 years were admitted and followed up for 95.3 (14-197) months. DI was noted in 12 patients in pretreatment and 16 in posttreatment regardless of tumor size. We carried out the replacement of GH in all 8 patients, presenting the symptoms under 15 years of age. Gonadal or gonadotropic, thyroid and adrenal hormones were replaced in 9, 12 and 15 patients, respectively. Patients with large tumor compressing chiasm or hypothalamus needed hormonal replacement such as gonadal or gonadotropic and thyroid hormones more frequently (<0.01) than those with small one. In addition, two patients with a small tumor at the pituitary stalk and the 3rd ventricle floor showed the improvement of secretion pattern in gonadotropins and ACTH after chemotherapy, although they later needed radiation therapy to control the tumor. Based on our study and review of literature, the endocrinological studies before and after treatment demonstrated that pituitary dysfunction present before treatment persisted or worsened even after tumor remission, except for patients with small and localized ones. The poor endocrine results is considered to be largely radiation-related. Chemotherapy alone seems to be insufficient to obtain complete response (CR). To avoid radiation related pituitary injury, combination of 24 Gy or less dosage of radiation and appropriate chemotherapy is essential. The earlier diagnosis by repeatedly using neuroimaging and serum and CSF tumor markers and earlier initiation of treatment, before irreversible pituitary-hypothalamic damage occurs, contributes to improvement of the outcome of pituitary functions in patients with neurohypophyseal germinomas [9)].

1998

Of seven patients with neurohypophyseal germinoma presenting with DI during the last 5 years, three patients showed no evidence of tumor at the onset of DI and were treated as “idiopathic” DI. Neurohypophyseal germinoma was eventually diagnosed in these three patients as the tumor became evident on sequential MR imaging studies and the patients were successfully treated with chemotherapy and radiation therapy. To delineate the clinical features of the occult neurohypophyseal germinoma, the authors analyzed endocrinological aspects and MR images in these patients and compared them with those in two patients with true idiopathic DI and four patients with overt neurohypophyseal germinoma and DI. Nine previously reported cases in the literature were reviewed. During the stage at which the germinoma gave no notable change on MR images, patients often displayed anterior pituitary dysfunction, particularly growth hormone (GH) deficiency, or an elevation of serum or cerebrospinal fluid human chorionic gonadotropin-beta. Preceding the appearance of an obvious tumor mass, a slight swelling of the pituitary stalk with loss of normal hyperintensity of the posterior pituitary lobe was a common finding on MR imaging. Central DI associated either with an enlarged stalk, decreased GH secretion, or an elevated serum human

chorionic gonadotropin-beta should prompt the diagnosis of an occult germinoma [10].

1991

Fujisawa et al., reviewed magnetic resonance (MR) images in seven cases of germinoma in the hypothalamoneurohypophyseal axis (HNA). The intrasellar portions were clearly identified in six germinomas. Two small germinomas of these six were located only in the neurohypophysis. The major parts of the four large germinomas were located below the optic chiasm, and the large intrasellar portions were demonstrated. The remaining one small germinoma was localized from the pituitary stalk to the third ventricular floor. These findings strongly suggest that the primary site of germinomas in the HNA is the neurohypophysis. In the four large germinomas, the tumor shape was similar to that of pituitary neuroendocrine tumor. The authors believe that age (limited to first three decades), symptoms (diabetes insipidus), MR findings (absence of normal hyperintense signal of the posterior pituitary on T1-weighted (T1WI) images, and homogeneous Hypointensity to the pons on T1WI images/isointensity on T2-weighted images are important in differential diagnosis [11].

Case reports

2016

Yoneoka et al., present a pediatric case of neurohypophyseal germinoma with a perifocal inflammatory reaction (PIR) with volume fluctuation caused by diagnostic radiation-induced regression (DRIR). On-target biopsy failed to confirm the histology because PIR hardly contained any germinoma cells. DRIR-related fluctuation of the tumor volume disguised germinoma as inflammation. They analyzed the cerebrospinal fluid (CSF) and detected a high level of placental alkaline phosphatase (PLAP), which demonstrated the neurohypophyseal lesion to be germinoma and brought the patient from successful radiochemotherapy up to complete remission. PIR adjacent to the germinoma (PIRAG) disappeared completely following radiochemotherapy, although it contained almost no germinoma cells. Examination of the CSF-PLAP level can complement the diagnosis of germinoma and will decrease the risk of misdiagnosis. Neurosurgeons should keep in mind PIRAG, DRIR, and the diagnostic value of CSF-PLAP when germinoma is suspected [12].

2015

A 19-year-old woman with a highly malignant intracranial germ cell tumor (GCT) that developed 14 years after treatment for neurohypophyseal germinoma. Magnetic resonance imaging (MRI) showed a large neurohypophyseal mass and a synchronous lesion in the pineal region. Plasma alpha fetoprotein was elevated to 3038 ng/mL. Although the tumor shrank and tumor marker levels normalized after chemotherapy and craniospinal irradiation, treatment was switched to oral etoposide for the residual tumor because of adverse events. MRI after oral etoposide introduction showed additional tumor shrinkage for 27 months after the onset of the second tumor. To the best of the author knowledge, this is the longest interval between germinoma onset and the development of highly malignant recurrent GCT to be reported in the English-language literature. Oral etoposide prevented regrowth of the GCT, which has a poor prognosis, and decreased the size of the residual tumor [13].

2012

Terasaka et al., report an unusual case of neurohypophyseal germinoma with abundant fibrous tissue and clival invasion that was initially misdiagnosed as lymphocytic hypophysitis. A 40-year-old woman presented with diabetes insipidus and panhypopituitarism after delivering her second son and which lasted for 4 years. Magnetic resonance imaging showed the intrasellar mass extending to the suprasellar region with enlarged pituitary stalk. The mass was heterogeneously enhanced and invaded the clivus. Biopsy of the intrasellar mass was performed via the trans-sphenoidal route, and histological examination revealed marked fibrous tissue and infiltration of lymphocytes, with no evidence of tumor cells. Lymphocytic hypophysitis was the initial diagnosis, and corticosteroid therapy was begun. Despite intensive treatment, the lesion enlarged and clinical symptoms worsened 2 weeks after surgery. Subtotal removal of the mass was performed, and a second histological examination revealed typical findings of the germinoma. Subsequently, the patient underwent chemoradiotherapy, and complete remission was achieved. Histological diagnosis is sometimes incorrect in fibrous tumors at the sellar region, and biopsy from several points is strongly recommended for this entity [14)].

2008

Neurohypophyseal germinoma in a young woman [15)].

2007

Fukushima et al., encountered a rare case of neurohypophyseal germinoma with a prominent granulomatous reaction, which invaded the right cavernous sinus. The neuroimaging and histopathology features in this case were unique, distinguishing it from other types of suprasellar lesions. A 13-year-old boy presented with loss of appetite and polyuria; both symptoms were present for 1 year, and headache, general fatigue and blurred vision present for the prior 2 months. On admission, neurological examination indicated bitemporal hemianopsia and optic atrophy. Endocrinological exam showed panhypopituitarism. Tumor markers such as alpha-fetoprotein, human growth hormone, carcinoembryonic antigen, and placental alkaline phosphatase were negative. Brain CT revealed a suprasellar tumor with calcification. MR T(1)-weighted and T(2)-weighted images showed the tumor to be isointense to normal brain parenchyma and to be enhanced densely. The tumor also involved the right cavernous sinus, so that a biopsy was performed by the transsphenoidal approach. On pathologic examination of the specimen, typical large tumor cells with lymphocytic cell infiltration and prominent granulomatous reaction were observed. Neurohypophyseal granulomatous germinoma was diagnosed. Radiotherapy was performed with a total dose of 51 Gy and the tumor shrank remarkably. The patient returned to school under hormone replacement therapy [16)].

2006

A case of intracranial germ cell tumor that showed pathological changes from neurohypophyseal germinoma to mixed germ cell tumors consisting exclusively of undifferentiated sarcomatous component after radiochemotherapy. Three surgical specimens and autopsied brain from the patient were histologically examined. An initial specimen from the neurohypophyseal tumor was diagnosed as germinoma with a two-cell pattern. Five years later, after repeated radiochemotherapy, the second

specimen resected from the right temporal lobe showed mixed germ cell tumors consisting of the three components of germinoma, choriocarcinoma, and immature teratoma. Six months later after intensive radiotherapy, the right temporal tumor recurred and was surgically removed. The histological diagnosis was mixed germ cell tumors with abundant immature teratoma component. The patient died of uncontrollable tumor growth with repeated intratumoral hemorrhages. The autopsied brain showed sarcoma with angionecrosis. This pathological alteration indicated an increase in the sarcomatous component after undergoing various treatments [17].

2004

Yoshizawa et al., report the usefulness of a highly sensitive immune complex transfer enzyme immunoassay (ICT-EIA) to detect human chorionic gonadotropin (HCG)-beta and thereby the onset of neurohypophyseal germinoma in its active phase. A 14-year-old girl exhibiting arrested puberty was diagnosed with neurohypophyseal germinoma following observation for two years. This patient initially showed no signs of diabetes insipidus (DI). While ICT-EIA indicated concentrations of HCG-beta higher than normal in cerebrospinal fluid (CSF) and serum, the results obtained with conventional methods were negative. ICT-EIA was also useful to assess the efficacy of treatment [18].

2002

Endo et al., report a case of neurohypophyseal germinoma appearing as predominantly granulomatous reaction in the first histological examination. A 12-year-old boy presented with diabetes insipidus, panhypopituitarism, and bitemporal hemianopsia. Transsphenoidal exploration for the intrasellar mass lesion extending to the suprasellar region was performed in May 1999. Histological examination revealed granulomatous hypophysitis and corticosteroid therapy was initiated. Six months later, the lesion relapsed despite corticosteroid therapy. Subtotal removal of the lesion was performed via an anterior interhemispheric approach in December 1999. Histological examination revealed typical germinoma. Subsequently, the patient underwent irradiation of 20 Gy to the tumour site and 24 Gy to the whole brain. Magnetic resonance imaging confirmed tumour remission. We must consider the possibility of neurohypophyseal germinoma in patients with granulomatous hypophysitis which does not respond to corticosteroid therapy, and perform re-exploration for more specimens to achieve the correct diagnosis [19].

2001

A 9-year-old girl presented with polyuria, polydipsia, and growth retardation. Urinary and endocrinological examination indicated diabetes insipidus (DI) and growth hormone deficiency. No clear evidence of a mass in the hypothalamo-pituitary area was apparent on the first MRI scan. Follow-up MRIs and endocrinological examinations revealed that a tumor, arising from the stalk and posterior lobe of the pituitary gland, formed a mass and caused anterior pituitary function to deteriorate. Histologic diagnosis was germinoma based on open biopsy.

Radiologic findings in this case indicated the primary site of this intrasellar germinoma to be the hypothalamo-neurohypophyseal region, designating this a “neurohypophyseal germinoma.” [20].

1998

A neurohypophyseal germinoma occurring 8 years after total resection of a pineal mature teratoma is presented. The patient underwent total resection of a large pineal mass in 1987. Histologic investigation revealed a mature teratoma without any immature or germinomatous components. In 1995, he developed diabetes insipidus. Magnetic resonance imaging depicted an intrasellar mass extending to the floor of the third ventricle. A transsphenoidal biopsy revealed histologically pure germinoma.

The second neurohypophyseal germinoma was considered to be a de novo metachronous neoplasm rather than a recurrence of the original mature teratoma [21].

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