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Prolongation of Survival in Diencephalic Tumor by Surgery and Radiation

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Abstract A case of diencephalic syndrome in a girl is reported. Computed tomography revealed a midline low-density mass accompanied by ventricular dilatation. Preoperative hormonal examination showed a high level of serum growth hormone, a low level of serum prolactin and lack of diurnal variation in serum cortisol levels.

Several partial removals of the tumor and radiotherapy enabled the patient to survive for 12 years after onset. Histological examination revealed fibrillary astrocytoma, and the DNA histogram showed a diploid pattern. Combination of multiple surgical removal and radiotherapy thus appears useful for prolongation of survival in cases of diencephalic tumor.

Key Words : Diencephalic syndrome, Diecephalic tumor, DNA histogram, Hypothalamic tumor

Introduction

In 1951 Russell reported diencephalic syndrome, of which the cardinal clinical features were profound emaciation after initial growth acceleration, locomotor overactivity and euphoria (1). The syndrome is caused mainly by a tumor in the region of the hypothalamus (2). The several studies have shown inappropriate or paradoxical plasma growth hormone (GH) responses to hyper- and hypoglycemia and absence of a diurnal rhythm of GH and cortisol secretion (3, 4, 5, 6, 7, 8). The mean patient survival time from onset is reported to be about 3 years (2, 9). This paper describes a patient who survived for 12 years after onset of this syndrome and gives details of the clinical course, endocrinological parameters and data of flow-cytometric DNA analysis. The factors affecting long-term survival are also discussed.

Case Report

The patient was a 12-year-old girl, who was born on October 15, 1975, with a normal birth weight of 3030 g. She did well until 4 months of age, and then showed a decreased weight gain in spite of adequate feeding. Her pediatrician pointed out hyperacusis, nystagmus, abnormal ocular position and mental and physical retardation, and referred her to our department on February 7, 1977.

Physical status

On first admission at the age of 1 yr 4 mo, her body weight was 6 kg, height 69 cm, head circumference 45 cm and chest circumference 39 cm. She showed marked loss of subcutaneous fat, a pale body, dry skin and normal pigmentation (Fig. 1). The fontanella was open, measuring 3 x 2 cm, and its tension was normal.

Neurological findings

The patient had clear consciousness, hyperacusis, right abducens palsy and horizontal nystagmus. The pupils were isocoric and respond-

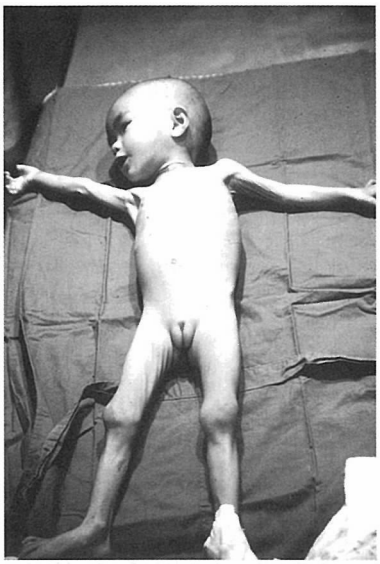

Fig. 1 Photograph of patient at the age of 16 months showing marked emaciation.

ed to light promptly. The optic fundi were intact. She had normal muscular tone, symmetric deep tendon reflexes and no abnormal reflex.

Laboratory findings

Hematological examination showed mild anemia and hyponatremia. Endocrinologically, the serum growth hormone basal level was 49 ng/ml and this decreased following L-DOPA administration (0.05 g p.o.) (Table 1). The basic serum prolactin level was 2.7 ng/ml. The responses of prolactin to TRH (60 μg i.v.) and L-DOPA (0.05 g p.o.) administration were decreased and absent, respectively. The serum cortisol level was 22.7 μg/dl at 8 : 00 a.m. and 19.7μg/dl at 6 : 00 p.m.. T_3 was 1.16 ng/ml and T_4 was 11.8μg/dl.

The lateral ventricular fluid had normal pressure, a high protein concentration (47 mg/dl) and no cells.

Radiographical findings

A plain X-ray skull film showed no separation of sutures, digital impression, sellar deformity or abnormal calcification. Cerebral angiography revealed a large mass effect and a small tumor stain, with feeding arteries from the anterior cerebral artery and middle cerebral artery. Central ventriculography demonstrated marked ventricular dilatation and obstruction of the foramen of Monro. Computed tomography (CT) showed a midline iso- and low density mass with marked enhancement, and bilateral ventricular dilatation (Fig. 2).

Table 1 Hormonal examination

T3 1.16 ng/ml
T4 11.8 μg/dl
Cortisol
8 : 00 a.m. 22.7μg/dl
6 : 00 p.m. 19.7μg/dl

TRH test (60μg i.v.)

	pre	30′	45′	
TSH	55.0	14.0	14.0	(μU/ml)
PRL	3.0	16.9	11.0	(ng/ml)

L-DOPA test (0.05 g p.o.)

	pre	60′	90′	120′
GH	49.0	65.0	68.0	26.0(ng/m
PRL	2.7	2.0	2.2	1.5(ng/ml

Surgical findings

A right frontoparietal craniotomy and transventricular approach were carried out on February 21, 1977. A soft, pinkish, easily bleeding and unclearly marginated tumor occupied the third ventricle and the head of the caudate nucleus, obstructing the foramen of Monro. These parts of the tumor were partially removed to allow communication between the two lateral ventricles for ventriculo-peritoneal shunting. Histological examination revealed fibrillary astrocytoma (Fig. 3).

Postoperative course

Postoperative radiation therapy using a beta-tron (total dose of 4000 rad during two months) was applied to the tumor site, and methyl CCNU 50 mg was administered orally every 6 weeks for two years. The tumor became small on CT scans, and the patient gained weight gradually to 8.5 kg over an 11-month period after the operation. She walked at the age of 1.5 years, and spoke simple words at 2 years.

Second admission

Follow-up CT on May 15, 1979, showed tumor recurrence in the same region. Radiation therapy with a total dose 4000 rad followed by methyl CCNU administration was therefore carried out.

Third admission

CT on May 14, 1981, showed tumor recurrence with a large cystic mass in the left temporal region, which was removed in two stage on May 28, and July 2, 1981.

Fourth admission

After December 1983, the patient suffered weakness of the right extremities. CT showed recurrence of the tumor with calcification, which was partially removed on June 18, 1984, followed

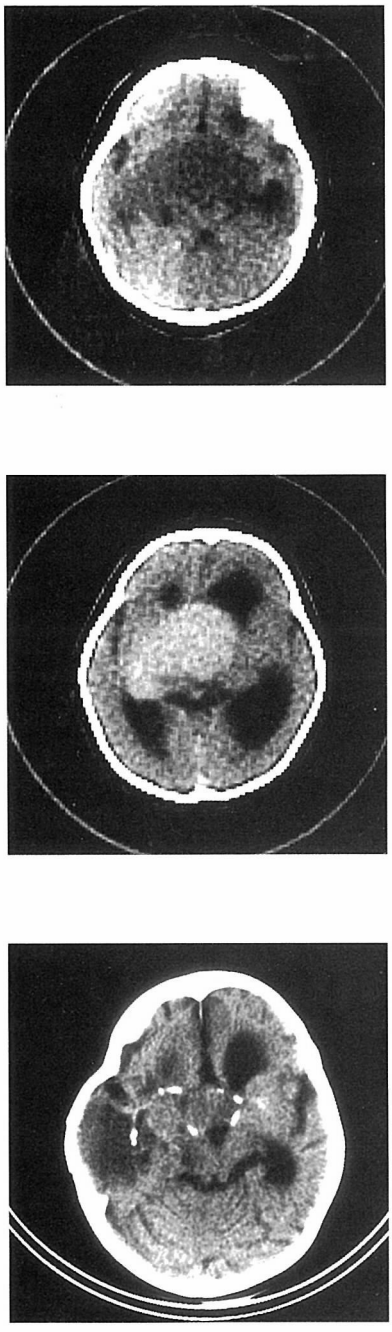

Fig. 2 The initial computerized tomography scans showed a midline low density mass which was markedly enhanced (a, b). And follow up scan showed temporal extension, cystic generation and calcification of tumor (c).

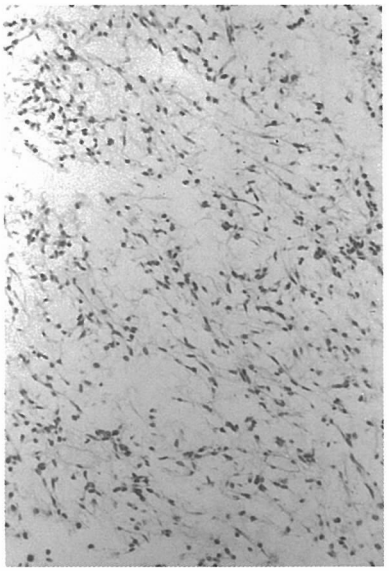

Fig. 3 Photomicrograph of the initial operative specimen showing fibrillary astrocytoma. H&E, x100.

by administration of ACNU 50 mg. The symptoms of right hemiparesis improved, allowing the patient to attend a school for mentally retarded children.

Fifth admission

After January 2, 1988, the patient began to have fainting attacks, headache and vomiting and CT showed regrowth of the tumor. On February 23, 1988, she suffered high fever. Laboratory data showed pancytopenia, bleeding tendency and hepatic dysfunction. Her bleeding tendency became uncontrollable and she died on March 15, 1988. Autopsy was done, and flow-cytometric DNA analysis was performed using ethanol -fixed BUdR-labeled specimens. No aneuploid line was observed and the populations of S, G 2 and M phase cells were very small (Fig. 4).

Discussion

Diencephalic syndrome was first reported by Russell in 1951. In 1976, Burr et al. reviewed 72 cases gathered from the world literature, and reported that the mean age at onset of the symptoms was 6.2 months (2). The main symptoms are emaciation, an alert appearance, increased vigor and euphoria. As a clinical feature for early diagnosis, Burr et al. described an alert appearance secondary

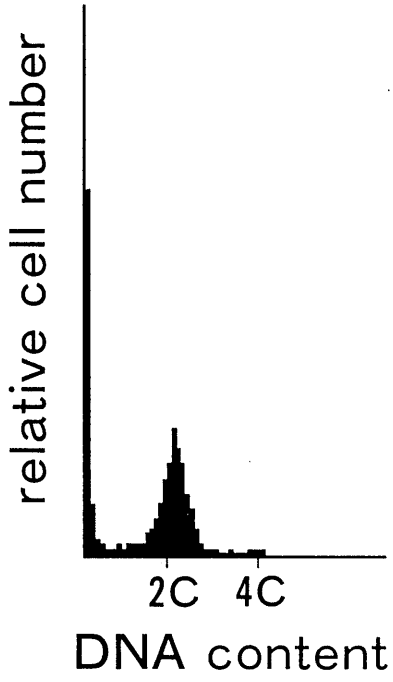

Fig. 4 DNA histogram obtained by flow cytometric analysis of nuclei from paraffin-embedded brain-tumor specimens. Histogram showed a unimodal DNA population (diploid pattern) and a low proliferating rate.

to lid retraction (Collier sign) (2). The majority of reported cases of diencephalic syndrome are caused by low-grade astrocytomas of the anterior hypothalamus or optic chiasm or nerves (1, 2, 3, 4, 10, 11). Therefore even when a patient has no sign of intracranial hypertension, computed tomography should be carried out for detection of any tumor.

Laboratory parameters were usually stated to be normal in the previous reports. In our present case, anemia and hypoalbuminemia were present, but these were probably due to the long interval from onset to admission, and the resulting malnutrition that occurred.

With regard to endocrinological parameters, Gamstrop et al. reported that the PBI, 17KS and 17 OHCS by ACTH test were normal (6). In the case reported by Smith et al., elevated plasma growth hormone was present, as in Pimstone's patient, and other hormones were normal (8, 12). Bain et al. pointed out diminished pituitary reserve, due to a hyporesponse of ACTH by the metopirone test (4). In our present case, however, disturbance of diurnal variation in plasma cortisol levels, a high basal value of serum growth hormone that was depressed by L-DOPA were recognized. The basal serum prolactin level was low and the response to TRH and L-DOPA were low and absent, respectively. T_3 and T_4 levels were normal. Our data, except for the prolactin level, were thus similar to those previous reports. From the results of the prolactin loading test, a disorder of hypothalamo-pituitary function seemed likely.

Burr et al. compared the survival times of untreated patients with those of patients treated by surgery and/or radiation therapy (2). The mean survival time of untreated patients was 12 months from onset of symptoms, in sharp contrast to the 91% of patients who, at the time of writing, were alive or had survived longer than 24 months following radiation alone or surgery plus radiotherapy. Markesbery et al. reported a patient who survived 12 years after tumor removal and irradiation (9). Although several authors have stated that astrocytomas at this site are relatively resistant to radiation therapy, the latter authors speculated that long-term survival could be attributed to tumor radiosensitivity. In our case, multiple partial removal of the tumor due to several recurrences, ventriculo-peritoneal shunt, postoperative irradiation and subsequent administration of methyl CCNU were carried out. As a result, after the first operation and radiation, the patient gradually gained weight and survived until 12 years old.

Fibrillary astrocytoma is considered to be a slow-growing tumor from the viewpoint of its clinical course and morphology. However, in some patients survival time is very short. Recently, we have used flow-cytometric DNA analysis for evaluation of cell growth, and have reported that tumors with aneuploidy correspond to cases diagnosed as malignant (13). In our present case, the DNA histogram showed a unimodal DNA population and a low proliferation rate. Thus the long-term survival of our patient was appar-

ently attributable to the slow growth, radiosensitivity and multiple surgical removal of her tumor.

The present case therefore indicates that long-term survival is possible for patients with diencephalic syndrome following multiple surgical resection and irradiation of the underlying neoplasm.

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