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Short communication

Long term survival in anti-Hu associated adult neuroblastoma

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ABSTRACT

We report on a young lady suffering from adult neuroblastoma and anti-Hu associated paraneoplastic encephalomyelitis (PEM) with a tumour free survival of nine years up to now. Treatment included tumour surgery, radiation, high dose chemotherapy, and stem cell transplantation. Serological testing demonstrated a marked decline in anti-Hu antibody titres under therapy, and subsequent disappearance of the antibody 31 months after second tumour resection.

1. Introduction

At age 23, this otherwise healthy technician experienced an episode of bilateral blurred vision. Ophthalmoscopic examination showed bilateral papilledema, pronounced on the right side. Visually evoked potentials (VEP) could not be elicited. Common causes of papilledema such as venous thrombosis, intracranial tumours or pseudotumour cerebri were excluded by brain magnetic resonance imaging (MRI), magnetic resonance angiography, and CSF pressure measurement. Brain MRI demonstrated as an incidental finding a reduced size of the cerebellum. Since no corresponding clinical signs were present at that time, cerebellar hypoplasia was assumed by her then treating physicians.

Eight months later, she developed slurred and scanning speech as well as uncoordinated and broad-based gait. At admission, marked gait ataxia and mild limb ataxia was noted as well as multidirectional gaze-evoked nystagmus. MRI showed marked cerebellar atrophy. Lumbar puncture (LP) revealed CSF-restricted positive oligoclonal bands (OCBs) and mild pleocytosis. Ophthalmoscopic examination now showed bilateral optic atrophy. Serological testing demonstrated serum antibodies against Hu (titre, 1:3200). Since this finding was not confirmed by a second laboratory, no further diagnostic measures were taken by her treating physicians at that time. Multiple sclerosis was assumed and treatment with high dose intravenous methylprednisolone (IVMP) was initiated, which resulted in temporary clinical improvement.

One month later, repeated attacks of sudden anxiety and marked aggravation of her speech and gait impairment led to readmission. During examination, a tonic seizure of the right-sided limbs occurred, followed by a generalized tonic–clonic seizure, after which the patient remained disorientated and somnolent and showed a status of automotor seizures [1]. An ictal EEG showed continuous left parieto–occipital seizure patterns compatible with a left parietal focal status epilepticus in that region. Treatment with valproic acid and lorazepam led to seizure control. LP again demonstrated OCBs and mild lymphocytic pleocytosis (10 cells/mm³). Nystagmus and gait impairment improved under high dose IVMP, and treatment with carbamazepine and prednisone was initiated.

The patient was subsequently referred to our hospital for further diagnostics. Neurological examination revealed mild visual impairment (right eye, 0.8; left eye 0.4); complex oculomotoric disturbance with upbeat nystagmus and a retraction myoclonus of both upper lids, horizontal and rotatory gaze-evoked nystagmus (GN), mild irregular spontaneous nystagmus, slow saccades, a complete ocular tilt reaction to the left; pale optic discs; anisocoria; gait ataxia, left-sided limb ataxia, and cerebellar dysarthria. No motor or sensory signs were present. MRI demonstrated cerebellar atrophy and, in addition, cortical and subcortical laminar hyperintensities on T_2-weighted and proton-weighted imaging involving the left insula, left claustrum and left parietal cortex without

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gadolinium enhancement (Fig. 1, columns 1–2). Cerebral ^{18}F-deoxyglucose–PET (FDG–PET) showed 15% hypermetabolism of the left insula and 10% hypermetabolism of the left parietal cortex, as compared to the contralateral homologous regions (Fig. 1, column 3). VEP could still not be elicited on the right side but were now normal on the left side. EEG showed left-temporal continuous slow activity and intermittent generalized slow activity but no epileptiform potentials. Serological testing confirmed serum anti-Hu antibodies (titre, 1:1920). No other paraneoplastic antibodies such as anti-Ri, -Yo, -Ma, -Ta, or -VGCC were found. LP showed OCBs and no pleocytosis. Vasculitis was ruled out by broad serological screening, MR angiography, and skin biopsy. Computed tomography of the abdomen was performed to address possible paraneoplastic aetiology and revealed two enlarged lymph nodes adjacent to the left adrenal gland. Elevation of urinary catecholamines was not found. Both para-aortic tumours were resected. Histological analysis documented poorly differentiated neuroblastoma characterized by atypical cell complexes with ovoid and hyperchromatic nuclei, partly rosette shaped with fibrillary matrix, increased mitosis, giant tumour cells with bizarre nuclei, areas of necrosis. Tumour cells expressed neuron-specific enolase (NSE) and synaptophysin. Single eosinophilic cells showed low-level gangliocytic differentiation.

The tumour was subsequently treated with six cycles of adriamycin and ifosfamide over the next 5 months. After the second and fourth cycle, stem cells were harvested, and after the sixth cycle high dose chemotherapy (carboplatin 200 mg/m², isosfamid 2000 mg/m², etoposide 2 × 100 mg/m² d1–5) with subsequent stem cell transplantation was performed. After the third and sixths cycle, continuous and marked improvement of gait and oculomotor function was noted. Correspondingly, the laminar T_2-weighted hyperintensity of the left insula as documented by MRI as well as the left-sided hypermetabolism as documented by cerebral FDG–PET gradually remitted (Fig. 1, columns 4–5). Anti-Hu antibodies were still detectable after the sixth cycle, albeit at lower level (1:480).

Six weeks after stem cell transplantation, however, her gait impairment worsened markedly and falls occurred. Dose reduction of carbamazepine resulted in dramatic increase in seizure frequency. In parallel, cerebral FDG–PET demonstrated substantially increased hypermetabolism in the left insula (Fig. 1, column 6). Abdominal CT confirmed tumour relapse. A second resection of the left adrenal region was performed and a thermal tube for thermometry in regional hyperthermia was placed. Histological examination revealed residuals of the former poor differentiated neuroblastoma (0.5 cm) and, anatomically separated, a ganglioneuroma (3.8 cm) with neurofibromoid matrix and proliferation of Schwann cells; mainly mature gangliocytes with satellite cells, prominent nucleoli and occasionally pigmented cytoplasm; small foci of calcification; and mild perivascular lymphocytic infiltration. After resection, one cycle of chemotherapy (etoposide, ifosfamide, adriamycin) was applied. Due to leukopenia, chemotherapy was discontinued and radiotherapy (45 Gy) was performed three months later.

Shortly after resection, gait and speech impairment started to improve and good seizure control was achieved under the previous carbamazepin dose. Cerebral FDG–PET hypermetabolism was not detectable anymore

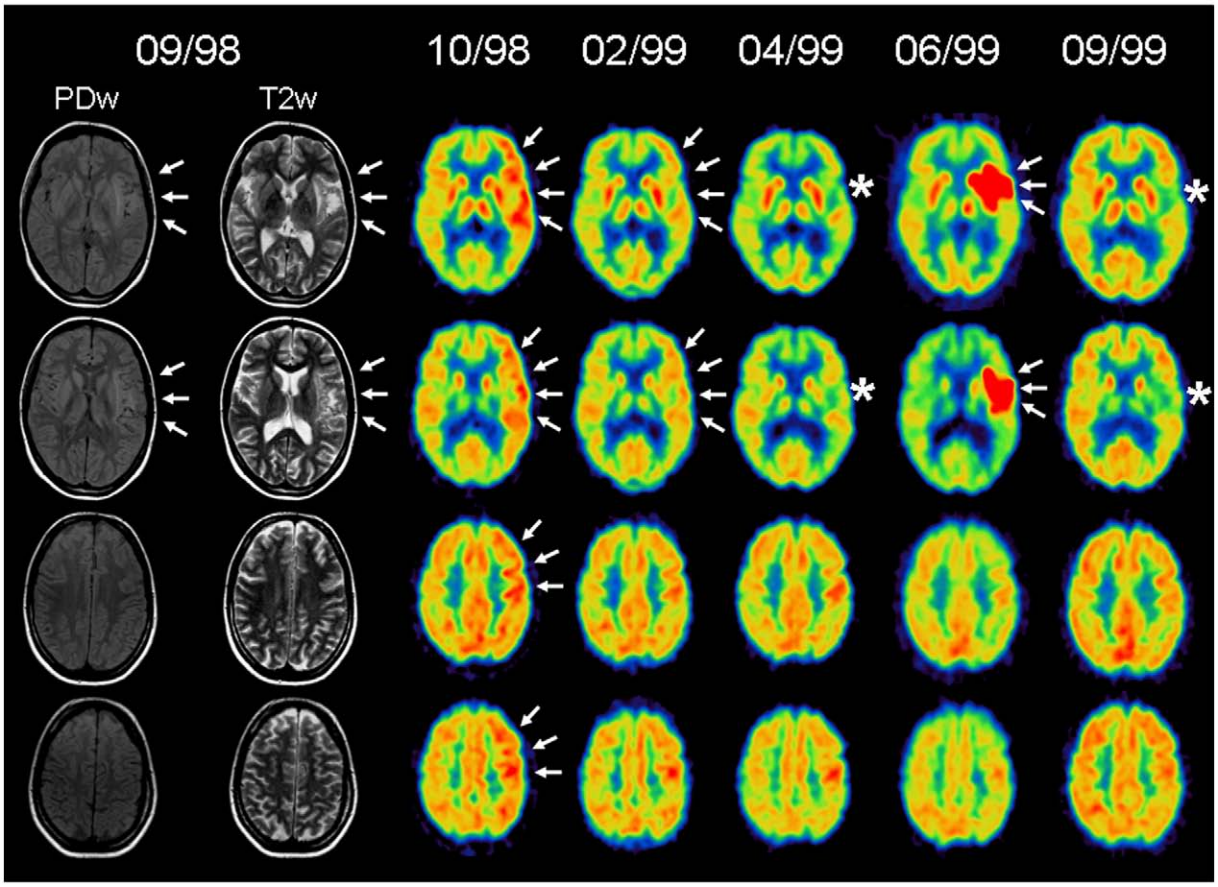

Fig. 1. Cerebral MRI sequences (proton- and T_2-weighted sequences; column 1 and 2, respectively) showing cortical and subcortical laminar hyperintensity involving the left insula (arrows) and left parietal cortex (arrows). Columns 3–7: corresponding FDG–PET findings between October 1998 and September 1999. Third column: hypermetabolism of the left fronto-parietal cortex (arrows) and in particular of the left insula (+15% compared to the corresponding area of the right hemisphere) before chemotherapy (compatible with a left parietal focal status epilepticus in that region); fourth column: hypermetabolism of left insula gradually remitted (slight hypermetabolism: +4% [arrows]) during chemotherapy; fifth column: slight hypometabolism of left insula (−3% [asterisk]) before high dose chemotherapy; sixth column: massive hypermetabolism of left insula (arrows), indicating an early tumour relapse (+131%) before second resection; last column: hypometabolism (−16%) of left insula (= defect after paraneoplastic encephalitis) after second resection of the neuroblastoma recurrence (asterisk).