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Somatostatin receptor imaging of olfactory neuroblastoma

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Abstract
Neural-crest tumours, including neuroblastomas, express somatostatin receptors. This can be shown by radionuclide labelling of octreotide, a somatostatin analogue. Studies on imaging with this substance have dealt with childhood neuroblastomas. Olfactory neuroblastoma (aesthesioneuroblastoma) is a rare tumour in which somatostatin receptor content has not been analysed, nor have radionuclide methods for diagnostic purposes been described. We report a case of olfactory neuroblastoma, in which scanning with ^{111}In-labelled octreotide was performed. A strong uptake was seen at the base of the skull. This was confirmed as a recurrent tumour by magnetic resonance (MR) imaging. Uptake was also observed in the neck and chest, indicating extensive spread of the disease.

Somatostatin receptor expression has been shown to correlate with prognosis in childhood neuroblastoma. The accuracy of labelled octreotide in the diagnosis of olfactory neuroblastoma indicates that it might be useful in radionuclide therapy of patients with advanced disease, when no other treatment modalities are available.

Key words: Somatostatin; Octreotide; Neuroblastoma, olfactory

Introduction

Somatostatin (SST), a polypeptide consisting of 14 amino acids, inhibits the secretion of somatotropin (growth hormone) by the pituitary gland. SST is mainly produced in the hypothalamus, but several other tissues have demonstrated high amounts of SST and SST-like peptides. These include the gastrointestinal tract, the cerebral cortex, the spinal cord, the brainstem and the pancreas (Gottesman *et al.*, 1982). Somatostatin receptors are expressed on certain neural crest-derived tumours, including pancreatic islet cell and carcinoid tumours, medullary thyroid carcinomas, pheochromocytomas, and paragangliomas (Moertel *et al.*, 1994). SST has been shown to have many different biological activities, such as being a neurotransmitter within the central nervous system, a neurohormone inhibiting somatotropin secretion, and a paracrine factor within the pancreatic islets (Gottesman *et al.*, 1982). The very rapid action of somatostatin suggests a mechanism of action via plasma membrane receptors. SST is unstable *in vivo* and has a half-life of only three minutes in man (Bethge *et al.*, 1981). Octreotide is an octapeptide, which has an identical bioactive site to that of SST. Because of its stronger stability *in vivo*, octreotide is frequently used for treatment of hormone-producing tumours (Kvols *et al.*, 1986). Radiolabelled octreotide has been used for imaging of tumours containing SST receptors. Such tumours include growth hormone-producing pituitary adenomas, meningiomas, malignant breast tumours, astrocytomas, medulloblastomas, neuroblastomas and oat cell carcinomas of the lung (Krenning *al.*, 1989). SST receptor expression in olfactory neuroblastoma has not been studied. This tumour type, unlike neuroblastoma in other sites in the body, arises in adulthood. Because of this, and because of its rare occurrence, the diagnosis can sometimes present difficulties (Lund and Milroy, 1993). We present a case of olfactory neuroblastoma with strong expression of SST receptors, demonstrated by gamma-imaging. The correlation between receptor expression and tumour grade, as well as the implementation for using 'receptor-radionuclide' therapy are discussed.

Case report

A 53-year-old female was diagnosed as having a tumour in the left nasal cavity in 1988. No intracranial involvement was observed on CT. Surgical removal by a sublabial approach, including rhinotomy, maxillary antrotomy and medial maxillectomy, was performed. Histopathology revealed olfactory neuroblastoma. A local recurrence was removed seven months after the initial operation. Post-operative radiation therapy was given to the area of the primary tumour. Neck metastases occurred in 1991, and a radical neck dissection on the left side was performed, followed by radiation therapy to the neck. A recurrent metastasis was removed at the beginning of 1995. In May 1995, a radionuclide octreotide scanning was performed by injecting 144 MBq of ^{111}In-labelled pentetreotride (Octreoscan®, Mallinckrodt, Petten, The Netherlands) to evaluate further tumour recurrence and spread to distant organ locations. Gamma-imaging was performed four hours, 24 hours and 48 hours later. The patient gave an informed consent before the injection.

Figures 1a and 1b show gamma-images 48 hours after intravenous injection of the tracer. The injected radiation activity was 144 MBq. A very strong uptake is seen in the region of the skull base near the foramen magnum (Figure 1a). Tumour-to-background ratio on the gamma image exceeds 6:1. Uptake is also seen in the lower neck region and upper mediastinum, as well as in the lower part of both lungs (Figure 1b). The involvement of the lungs was previously unknown. An image confirms the site of the

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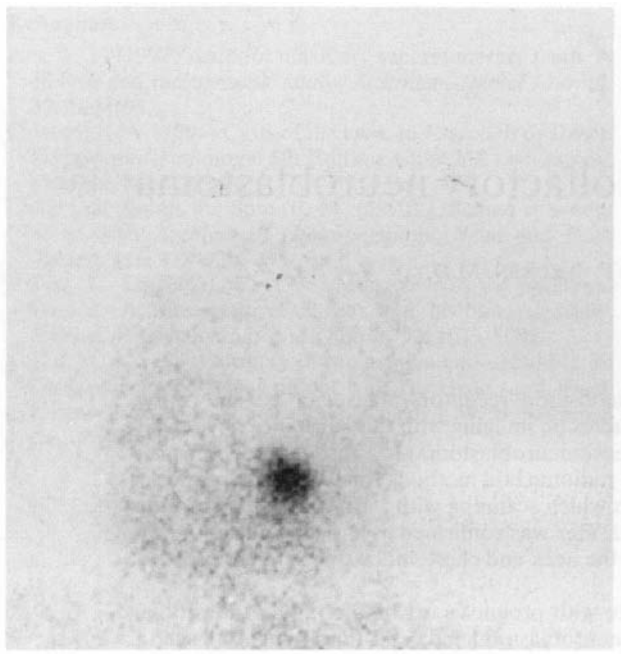

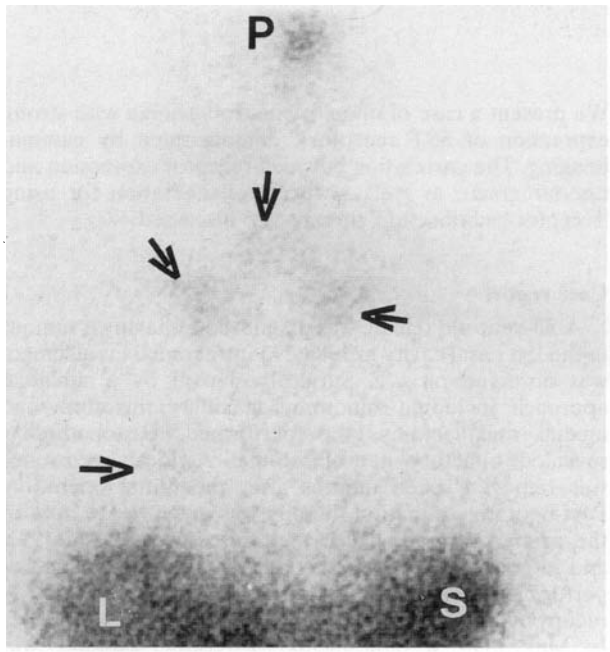

(b)

FIG. 1

a) Somatostatin-receptor image (left lateral view of head and neck) 48 hours after injection. Extremely strong uptake is seen at the base of the skull. b) A-P projection (head, neck and chest) shows the same primary tumour (P) paramedially on the left side at the skull base. Metastatic uptakes are also seen in the upper mediastinum and both lungs (arrows). Liver (L) and spleen (S) visualise normally in the lower part of the figure.

skull base tumour to the region near the foramen magnum on the left side (Figure 2). MRI also confirmed the neck, mediastinal and lung uptakes to be of tumour origin. Currently the disease has extensively progressed, and the patient is in a terminal condition.

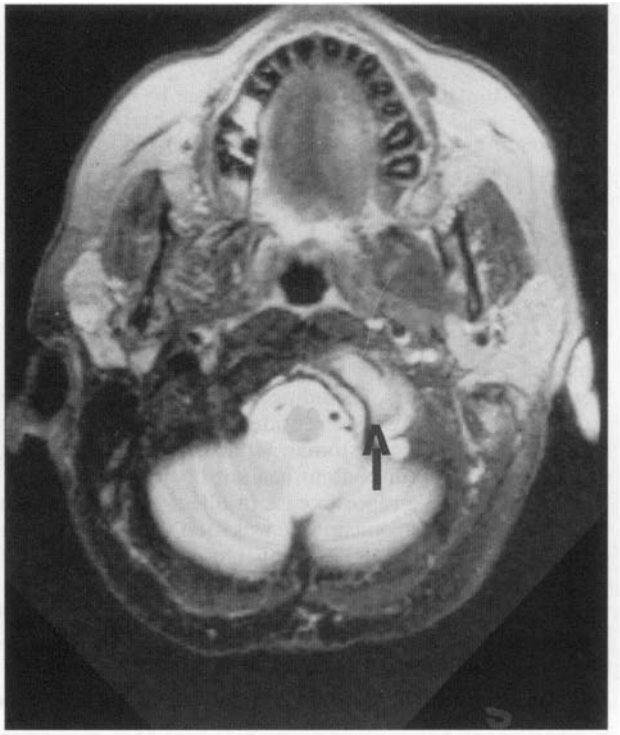

FIG. 2

Magnetic resonance image of skull base region confirming recurrence of neuroblastoma (arrow), seen on gamma images in Figures 1a and b

Comment

Somatostatin scintigraphy is an example of receptor imaging, in contrast to, e.g. radiolabelled antibody imaging. Uptake of octreotide by SST receptors in childhood neuroblastoma has been studied both in cell culture (O'Dorisio *et al.*, 1994a), in nude mice xenograft tumours (Manil *et al.*, 1994), and in tumour samples, using autoradiography (Moertel *et al.*, 1994). All these studies show the presence of SST receptors in this type of tumour. Furthermore, there is indication of a positive correlation between favourable prognosis (higher survival rate) and receptor uptake of octreotide (Moertel *et al.*, 1994; O'Dorisio *et al.*, 1994b). In neuroblastoma cell lines representing tumours of high differentiation (grade I and II) somatostatin receptor binding was seen in six of seven, whereas only in seven of 19 low differentiation (grade III and IV) tumour cell lines (O'Dorisio *et al.*, 1994b). Correlation between somatostatin receptor expression with survival was statistically significant in a group of 30 children with neuroblastoma (Moertel *et al.*, 1994). Twenty-three of these tumours expressed somatostatin receptors, and had a more favourable prognosis. These data indicate that octreotide interacts with high affinity somatostatin receptors to modulate signal transduction and regulate proliferation in neuroblastoma cell lines. The data also suggest that somatostatin receptor expression may be an independent prognostic factor in primary neuroblastoma tumours.

There is no previously reported evidence in the literature of SST receptors in olfactory neuroblastoma. Our case demonstrates that SST receptors are strongly expressed in this type of tumour. This rare malignancy is surgically challenging and length of survival varies. In a study by Lund and Milroy (1993) 71 per cent patients were alive with >5 years follow-up. Survival ranged from death

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of disease at 10 months to alive without disease at 180 months.

Besides using somatostatin receptors for diagnostic purposes in tumour patients, they have also been suggested for therapeutic purposes (O'Dorisio *et al.*, 1994b). The strong uptake of ^{111}In-octreotide indicates that radionuclide therapy may be possible in olfactory neuroblastoma. By increasing the injected radioactivity to levels exceeding 1 GBq, killing of tumour cells could be possible. In fact, first clinical results with ^{111}In-octreotide show potentials as somatostatin-receptor radiopharmaceutical in insulinoma, islet cell carcinoma, medullary and lung cancer (Biersack *et al.*, 1992). We have developed this type of therapy in squamous cell carcinoma of the head and neck (Kairemo *et al.*, 1995; Kairemo *et al.*, 1996). For this purpose we used ^{111}In combined to bleomycin, which has a strong tumour-seeking behaviour. Using octreotide as a vehicle to bring radiation to the tumour could be a future option in treatment of neuroblastoma. This type of treatment needs further development before 'receptor-radionuclide' therapy is possible.

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