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Anaplastic astrocytoma associated with human growth hormone administration

Sir: Laron and Josefsberg[1] reported two deaths out of 166 children treated with human growth hormone (HGH). One of these died from a large cystic brain tumour shown on angiography; however necropsy was not performed and no histological diagnosis made. They called for further reports of neurological disease and deaths encountered in other patients on HGH therapy.

In Glasgow, an 18 year old male who had been treated with HGH for seven years, later developed an astrocytoma. Only 35 cases of astrocytoma have been recorded in the West of Scotland between 1974–1983 in the 15–25 year age-group (personal communication. West of Scotland Cancer Surveillance Unit). This patient was started on HGH therapy at age 9 years in 1977, in a dose of 4 I.U. three times weekly until 1984. In 1986 he presented with a ten day history of headache, malaise, nausea and vomiting. On examination he had papilloedema, and a computer tomography brain scan revealed a large cystic tumour deep in his right parietal lobe. Major craniotomy was not recommended as this was liable to cause severe neurological deficit, and a limited biopsy procedure was performed, revealing anaplastic astrocytoma on histology. He deteriorated rapidly and died.

Natural HGH has been withdrawn in both UK and USA because of its association with Creutzfeldt-Jacob disease,[2] but association with astrocytoma has not previously been described.

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Skull base chondroma presenting in pregnancy

Sir: We present the case of a patient with multiple chondromatosis and rapidly evolving cranial nerve palsies during two successive pregnancies. No skull lesion had been apparent previously. Symptomatic cure followed partial excision of a chondroma arising from the skull base. A subsequent pregnancy proceeded uneventfully to term.

A 29 year old woman complained of left facial numbness and pain after 5 weeks amenorrhoea. Three weeks later she developed a partial left ptosis which became complete after another week.

At the age of 14 she had noticed swellings on the hands and feet, several of which required curettage for cosmetic reasons or because of local trauma. These were benign enchondromata. Asymptomatic lesions were also apparent radiologically in the limbs and in several ribs. Her first pregnancy at the age of 21 yr had been complicated by pre-eclampsia but ended in normal delivery of a healthy baby and the second pregnancy had been terminated "thera-peutically" in the first trimester. Fifteen months before this admission she had complained of numbness of the left side of her face after 8 weeks amenorrhoea; this resolved following a spontaneous abortion. No neurological symptoms occurred during her normal menstrual cycle.

Examination revealed scars, localised hard swellings over several long bones and deformity of the left forearm. There was a complete left third nerve palsy and she had reduced sensation in the ophthalmic territory of the left trigeminal nerve, a reduced corneal reflex, anaesthesia of the two lower divisions and an ipsilateral trigeminal motor palsy. Skull radiographs, CT scan and carotid angiography revealed an enlarged foramen ovale, irregularity of the petrous bone, expansion of the clivus and dorsum sellae, a soft tissue mass in the posterior nasopharynx and narrowing and displacement of the internal carotid artery.

Despite the well established benign nature of the limb lesions urgent exploration of the cranial lesion was felt to be indicated as its rapid presentation and progression raised the possibility of malignancy. The pregnancy was terminated on medical advice (with some reduction in facial pain) and one week later craniotomy was performed, revealing a pinkish-grey tumour extending into the cavernous sinus and through which the third, fourth, fifth and sixth cranial nerves passed. An extensive internal decompression of the partly mucinous tumour was undertaken. Histology confirmed a benign chondroma with no features of malignancy; there was cellular enlargement and a swollen matrix.

Partial resolution of the third nerve palsy occurred within 3 days and there was full return of sensation in the two lower trigeminal divisions by one week. Further recovery took place and after 9 months the only residual complaint was of infrequent paraesthesiae of the left cheek without any abnormal signs. One year later she expressed a wish to become pregnant again, provoking mixed reactions from her medical advisers. The consensus was in favour of pregnancy before a natural increase in cell numbers and residual tumour bulk could again cause symptoms. Since that time she had an uncomplicated pregnancy, delivering a healthy baby.

Chondromata of the skull are uncommon. Arising from synchondroses, they are slow growing, often solitary and usually benign. An increased tendency to undergo malignant change had been suggested when they occur in patients with multiple chondromatosis (Ollier's disease, dyschondroplasia).[1] Lesions in the skull base usually present with progressive cranial nerve palsies, while those in the vault may act as mass lesions.[2–6] They are said to be more common in females.[7] The rapid progression of our patient's symptoms was, we believe, due to tumour enlargement under the influences of pregnancy. This is an established feature of intracranial tumours and most histological types can behave in this way, the commonest being astrocytoma, meningioma and neurofibroma.[8]

The mechanism causing rapid enlargement of tumours in pregnancy is the subject of debate. Although the physiological

changes of pregnancy are undoubtedly responsible, the local phenomena require explanation. King[9] suggested that engorgement of blood vessels causes tumour expansion, while Weyand[10] proposed that it is due to an increase in intracellular fluid supporting this hypothesis with two cases explored during pregnancy which appeared histologically to have "foamy and swollen" cytoplasm. We feel that the features of this case partly support Weyand's theory, the enlarged cells and swollen matrix implying an increase in both intracellular and extracellular fluid.

The differential diagnosis of intracranial tumours presenting in pregnancy must include arteriovenous malformations and eclampsia.[11] We have found one other report of an intracranial chondroma presenting in pregnancy; a patient with a three month history of seizures and a hemiparesis commencing in the third trimester.[12] The recurring nature of this patient's symptoms in two of her pregnancies is of some interest; this phenomenon was also described by Bickerstaff who reported two patients with meningiomata, both of whom had symptoms in successive pregnancies.[13] Progressive or recurring neurological symptoms in pregnancy are considered possible manifestations of an intracranial tumour but it should also be recognised that rapid progress may be the result of pregnancy, not of malignancy.

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Recurrence of Cushing's disease due to corticotrophe hyperplasia following transsphenoidal hypophysectomy

Sir: Over the last 15 years the treatment of pituitary-dependent Cushing's syndrome has changed, in many centres, from bilateral adrenalectomy to total hypophysectomy, partial hypophysectomy, or selective adenomectomy, performed by the transsphenoidal route.[1 2] Most results have been encouraging but Burch[3] suggested that recurrence is more likely if the pituitary histology shows corticotrophe hyperplasia. However, although it is recognised that such cases may not be cured by radical hypophysectomy[4] there have been no reports of late recurrence following an apparently successful initial outcome. We describe a patient with a radiologically normal pituitary fossa, in whom pituitary-dependent Cushing's syndrome due to corticotrophe hyperplasia recurred 42 months after apparently successful treatment by radical transsphenoidal hypophysectomy.

A 32 year old woman presented with acne, hirsutes, amenorrhoea, easy bruising, truncal striae, weight gain and proximal myopathy. Loss of diurnal plasma cortisol variation and increased 24 hour urinary excretion of oxogenic steroids, which did not suppress during the administration of 0·5 mg dexamethasone 6-hourly, confirmed the diagnosis of Cushing's syndrome. Further investigation showed a raised plasma adrenocorticotrophic hormone (ACTH) concentration (118 ng/l, normal range (10–80), partial suppression of 24 hour urinary oxogenic steroid excretion by 2 mg of dexamethasone 6-hourly (132 μmol/24 hr to 84 μmol/24 h and increased excretion of urinary oxogenic steroids during the administration of 750 mg of metyrapone 4 hourly (134 μmol/24 h to 320 μmol/24 h. During insulin induced hypoglycaemia the increment in plasma cortisol concentration was subnormal and the plasma growth hormone (GH) response absent. Skull and chest radiographs, computed tomography of the pituitary fossa and abdomen and plasma electrolytes were normal. These data suggested a diagnosis of pituitary-dependent Cushing's syndrome and a radical transsphenoidal hypophysectomy was performed by the trans-septal, trans-ethmoidal route. At operation soft material and tough tissue were seen, but as no adenoma was identified, the pituitary fossa was cleared, leaving 1–2 mm of normal tissue around the stump of the pituitary stalk. Histology of the pituitary revealed diffuse corticotrophe hyperplasia without Crook's hyalinisation. Immunoperoxidase staining for ACTH confirmed this diffuse hyperplasia with nodular condensations of positively stained cells. A discrete adenoma was not seen.

The features of Cushing's disease resolved, regular menses returned, her weight fell by 30 kg and repeated 24 hour urine collections for oxogenic and oxosteroid excretion were normal. When glucocorticoid replacement therapy was tailed off her diurnal cortisol rhythm was normal (0900 hours 500–600 nmol/l, 2400 hours < 240 nmol/l) and dynamic tests of endocrine function showed that no replacement therapy was required. She remained well for 42 months, when she became hypertensive with recurrence of hirsuties, acne and truncal obesity. Relapse of Cushing's disease was confirmed by an elevated 24 hour urinary free cortisol excretion (1200 μmol/24 h, normal range 100–330), a plasma cortisol of 662 nmol/l at 0900 hours following the administration of 1 mg of dexamethasone at 2400 hours, and a plasma ACTH concentration of 55 ng/l. Skull radiographs, computed tomography of the pituitary fossa and plasma electrolytes remained normal and again there was no evidence for an ectopic source of ACTH production.