Diencephalic syndrome with long-term survival

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SUMMARY

Infants and young children with the diencephalic syndrome exhibit a normal activity level despite profound marasmus. Investigation reveals an intracranial tumour and evidence of endocrine dysfunction. The condition is easily missed in Third World countries with a high prevalence of nutritional marasmus. The advent of computer tomography and magnetic resonance imaging has simplified diagnosis.

The syndrome was diagnosed in 1981 in a boy of 20 months who had a large hypothalamic tumour. Initial endocrine studies revealed very high growth hormone levels. After radiotherapy, these levels reverted to normal for a time but have subsequently declined in keeping with a state of hypopituitarism. The boy's long-term survival has afforded an opportunity for study over eight years.

During this time, growth has been slow but sustained. There has been some fall off in intellectual capacity.

Characteristic features of the diencephalic syndrome are normal activity and a state of euphoria in a profoundly marasmic child. Investigation reveals the presence of an intracranial tumour and evidence of endocrine dysfunction. Though there are earlier references, the condition first came to medical attention at the annual meeting of the British Paediatric Association in 1951 when Russell described the typical features. In Third World countries where childhood marasmus is common, the syndrome is easily overlooked. The present report concerns a boy who has been closely followed for more than eight years.

CASE HISTORY:

G.A. was referred from a rural hospital at the age of eighteen months because he was failing to thrive despite a good diet. Pregnancy and confinement had been uncomplicated with birth weight of 3.5 kg. Early motor development followed a normal pattern. On examination, his bright and alert attitude provided a striking contrast to his gaunt wasted appearance with complete absence of subcutaneous fat (Figure 1).

Figure 1: GA at age of 18 months.

His weight (6.4 kg) was less than 60 pc of expected weight for age. His height (76 cm) and head circumference (46 cm) were just below the 3rd centile. Rapid coarse pendular nystagmus was noted. There was no papilloedema. Systematic examination did not reveal any other abnormality. Bone age was appropriate.

A C.T. scan showed a large midline hypothalamic tumour with no evidence of calcification or hydrocephalus (Figure II).
Haemoglobin, serum albumin, glucose, sodium, potassium, urea, alkaline phosphatase and transaminase levels were all normal. Fasting triglyceride level was elevated (4.05 mmol/l). Thyroid stimulating hormone (TSH) level was within the normals range as was basal prolactin level. Early morning and midnight cortisol levels were normal with no loss of diurnal variation. Stimulation with gonadotrophin releasing hormone (GnRH) produced normal increases in follicle stimulating (FSH) and luteinizing hormone (LH) levels. Basal growth hormone (GH) level was in excess of 1000ng/ml. There was an inappropriate drop following administration of propranolol and L dopa. This suggested severe impairment of normal pituitary regulation. (Figure III)

The patient's tumour was deemed inoperable. He received 4500 Rads of cobalt radiotherapy administered over 12 weeks.

He has been reassessed at regular intervals over the past eight years. Following treatment growth velocity was reasonable for some two years. Thereafter, a significant deceleration occurred. This is clearly depicted in growth charts. (Figure IV)

Growth hormone levels in response to insulin induced hypoglycaemia and clonidine stimulation were markedly subnormal 18 months after radiotherapy and have remained at a very low levels (Figure III).

With return of subcutaneous fat the child lost his former cachectic appearance. At three and half years, speech was well developed. He was potty trained and able to ride a tricycle. Developmental assessment at 73 months showed age appropriate gross motor, fine motor and social development with language function at approximately 60 month level. Formal
psychometry revealed an I.Q. of 83. When he attended the hospital at the age of eight, the child's optic discs were pale and visual acuity was R 3/3; L 6/60. C.T. scan showed calcification in the hypothalamus and basal ganglia.

His most recent hospital admission was in October, 1988 shortly after his ninth birthday. He remained alert and keen to learn but had not been promoted at the end of his first year of formal schooling. He did not report any subjective visual symptoms.

Clinical examination revealed no new abnormality. Bone age was six and a half years. Magnetic resonance imaging showed a large mass extending form the pituitary fossa to the level of the thalami. (Figure V).

_Figure V: MRI shoeing tumour extending from pituitary fossa to level of thalami_

Post irradiation changes were evident in basal ganglia. Serum chemistry and electrolyte levels were normal as were thyroxin and prolactin levels.

Normal diurnal cortisol variation was again demonstrated, but GnRH produced only slight increases in the levels of FSH and LH. Clonidine stimulation again produced a markedly blunted GH response. Treatment with biosynthetic growth hormone was considered but rejected because of the underlying pathology the child's intellectual level.

**DISCUSSION**

The diencephalic syndrome is an uncommon cause of marasmus even in developed countries. The happy and active demeanour of the child and a paucity of signs relating to the nervous system tend to conceal the underlying pathology. Early case reports indicate that the correct diagnosis was not made in some instances for many months (4,5).

The advent of computer tomography and magnetic resonance imaging has done away much of the earlier diagnostic and this investigation should be included in the work-up of a marasmic baby whenever reason for this nutritional state is not clear.

The tumour responsible for the diencephalic syndrome is usually a glioma and commonly an astrocytoma. In most instances, it is sited in the floor of the third ventricle or the optic chiasm, but a review of reported cases has shown that 9% of the tumours are located outside the diencephalon (6). Onset of symptoms occurs during the first year of life in 86% of cases. Without treatment, average survival is only 12 months though survival for eight and for 12 years after diagnosis has been reported (6).

The loss of vision, pendular nystagmus and progressive optic atrophy which occur in this condition can be attributed to direct tumour pressure on the optic pathways. Other characteristic features must come about through indirect mechanisms. GH secretion is regulated from the hypothalamus by two substances — growth hormone releasing hormone (GHRH) and somatostatin. The former has a stimulatory effect and the latter an inhibitory effect. Each of these hormones is secreted by a distinct population of tubero-infundibular neurons.

Elevated levels of GH demonstrated in the diencephalic syndrome may be due to selective impairment or destruction of somatostatin producing cells with consequent unopposed action of GHRH.

Raised levels of growth hormone brought about in this way could account both for continuation of linear growth and the absence of subcutaneous fat, for GH is a potent mobiliser of fatty acids. The effect which is characteristic of the syndrome could also be a result of tumour infiltration in the fronto-thalamo-hypothalamic circuits. This creates a situation similar to that achieved by the operation of prefrontal leucotomy.
Another explanation for the findings in this syndrome is suggested by knowledge that an increase in GH secretion occurs in response to endorphin and metencephalin. These substances are present in beta lipotrophin (BLPH) which has lipolytic properties. Increased secretion of BLPH due to tumour pressure could thus account for elevation in GH levels and also for lack of subcutaneous fat. The increased levels of endorphin and enkephalin would explain the patient's joie de vivre in the face of severe marasmus.

When first seen, the present case demonstrated typical features and biochemical findings. Radiotherapy has achieved long-term survival but at a cost. Initially, the child showed physical and biochemical evidence of reversal of the effects of the tumour. There was a return of subcutaneous fat and some increase in height. Cognitive function was satisfactory. With the passage of time there has been a fall off in intellectual performance. The velocity of height increase has decelerated and weight increase has fallen off dramatically. GH response to clonidine stimulation has diminished as have FSH and LH levels after GSH stimulation. The diurnal cortisol fluctuation is to date unimpaired.

These findings are in keeping with the sequential changes demonstrated during progressive hypothalamo-pituitary failure. Evidence of GH failure is followed by diminution in gonadotrophin secretion and then TSH decrease. ACTH is the last to fail.

Both intellectual fall off and hypothalamo-pituitary failure are well described following cerebral irradiation. As there have been no signs of raised intracranial pressure and the tumour mass has not increased in size it seems reasonable to hold radiation, rather than the tumour, chiefly responsible for the post-therapy changes in this case. Use of radiotherapy has nevertheless been fully justified for it has afforded the patient more than eight years of happy symptom-free life. A survival time of this duration, without treatment, is most unlikely.

REFERENCES


Urinary high density lipoprotein — a possible marker for glomerular proteinuria

ZAR GOMO

SUMMARY

High-resolution two-dimension electrophoresis technique for protein with silver staining was used to characterise urinary high density lipoprotein (HDL) apolipoproteins. Sequential ultracentrifugation method was used to isolate urinary lipoprotein particles of the same density as serum HDL. Immunostaining of electrobotted proteins further confirmed the presence of HDL-Apos in urine. HDL-Apolipoprotein A – 1, A – 11 and C were identified in urine of normal subjects, diabetic patients and patients with biopsy proven glomerular proteinuria. An in-house ELISA method was used to quantify urinary HDL-Apo A – 1. Selectivity indices were also determined.

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