Diencephalic Syndrome of Infantile Emaciation

Analysis of Literature and Report of Further 3 Cases

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Addy, D. P., and Hudson, F. P. (1972). *Archives of Disease in Childhood*, **47**, 338. **Diencephalic syndrome of infantile emaciation. Analysis of literature and report of further three cases.** Three children with diencephalic tumours are described, and an analysis of 45 cases from the literature together with our own 3 is presented. Boys are affected more frequently than girls (1·8 : 1) and the onset is during the first 12 months of life in 92% of cases. The main clinical features are emaciation, overactivity, pleasant disposition, and above-average height. The natural course of the disease is variable. Treatment is by radiotherapy. Operative intervention, except to relieve intracranial hypertension, is not usually indicated.

In 1932 Goebel described an infant who had bilateral nystagmus and was devoid of subcutaneous fat, though very tall. There was a history of occasional vomiting since birth. A glioma arising from the floor of the third ventricle was found at necropsy. This syndrome of infantile emaciation with a diencephalic tumour was not generally recognized, however, until Russell (1951) summarized his findings in 5 children. Almost simultaneously Weller (1951) described another child with the same condition. In 1957 Russell recorded his experience of a further 5 cases.

The present paper describes 3 children seen at Alder Hey Children's Hospital in the past 10 years, and reviews the recorded findings of 45 cases already described (excluding those of Russell which were not reported individually).

Case Reports

Case 1. A girl born to young healthy unrelated parents in June 1969. Delivery was assisted by forceps after an uneventful pregnancy. Birthweight 3340 g. She was breast-fed for 2 months, then given modified cow's milk. Cereals were introduced at 3 months.

Aged 5 months. She was seen by one of us (F.P.H.) because of poor feeding and no weight gain for a little over 2 months. There was no vomiting, no diarrhoea, and no noticeable polyuria. On examination she was a wasted, pale infant weighing 5400 g. In contrast to her emaciation she was alert and interested, and could raise her head from the pillow. There were no other signifi-

cant findings. She was not admitted to hospital but investigations showed faeces, normal appearance, no pathogens cultured; Hb 13·4 g/100 ml, white cell count normal; urine, pH 5·5, protein trace, no reducing substance, no deposit; blood urea 49 mg/100 ml; serum calcium 10·8 mg/100 ml. X-rays, abdomen normal, increased density at the ends of the radius, ulna, and proximal femora in keeping with hypercalcaemia. A few days later a calcium load test (Barr and Forfar, 1969) gave the following result: serum protein 6·3 g/100 ml; serum calcium, fasting and at 1, 2, 3, and 4 hours, 10·6, 10·8, 12·3, 12·1, 12·1 mg/100 ml. In the absence of any other probable diagnosis and in the presence of the x-ray changes and the slightly abnormal calcium load test, it seemed reasonable to try the effect of a low calcium diet, and this was given for 6 months. While on the diet there was a little gain in weight, but the length and head circumference continued to grow just below the 50th centile.

Aged 11 months. Further investigations showed normal urine, blood urea, serum calcium, full blood count, urine amino acids, faecal fat excretion, x-rays of chest, abdomen, skull, and ends of long bones; serum electrolytes were generally normal apart from one chloride estimation of 107 mEq. In view of the poor general response, normal diet was resumed. At first she fed well and gained a little weight. Dr. William Hamilton was then invited to review the problem.

Aged 12 months. The child was admitted to the Royal Hospital for Sick Children in Glasgow. Slight persistent hyperchloraemia was confirmed but the following investigations were normal: sweat chloride, blood urea, calcium and electrolytes, jejunal biopsy, and barium meal. The urinary pH was 5·5 after an ammonium chloride load. While in hospital the child had an avid

appetite but in the presence of the mother became grossly anorexic and refused all foods. Though the diencephalic syndrome was suspected, further investigations were impossible and the family returned to Liverpool.

In view of the observations made in hospital and the parental reluctance to allow further investigations at this time, it was decided to give the child a complete change of environment and partial separation from the mother.

Aged 17 months. She was admitted to a residential nursery where she was visited daily by her mother, but never at feeding times. After 9 weeks of this regimen there was no significant weight gain, even though she fed well.

Aged 1 year 7 months. Definite signs of a neurological lesion were detected for the first time, namely 'cracked pot' skull percussion note, minimal papilloedema of the right disc, and extensor plantar response on the right. The skull circumference was 49 cm. The deep tendon reflexes were brisk in contrast to the extreme muscle wasting and hypotonia. She continued to be alert and interested, and could use 3-word sentences. She was admitted to Alder Hey Children's Hospital where investigations showed: CSF clear, protein 20 mg, sugar 17 mg, chloride 135 mEq/l. X-ray of skull and wrist normal. Air encephalogram: marked dilatation of the lateral ventricles, no air passing into the third ventricle.

Investigations were continued in the Neurosurgical Unit at Walton Hospital under Mr. R. H. Hannah. On Ethiodan ventriculogram no contrast material could be made to enter the third ventricle which appeared to be obstructed by neoplastic tissue. A needle was introduced into the tumour and gelatinous material aspirated; this was reported (Dr. P. Buxton) to show appearances of a well-defined ependymoma. She was transferred to Clatterbridge Hospital for deep x-ray therapy (3500 rads in 3 weeks).

Since the radiotherapy there have been no further indications of raised intracranial pressure. The skull circumference remains within normal limits. Slowly she has gained muscular power and confidence. At the age of 2 years she could crawl actively and climb on to a couch and a month later took 3 steps without support. Her language development and general intellectual progress are within normal limits.

At 2 years 2 months she weighed 7711 g and was 75.6 cm tall.

Case 2. A girl born of healthy parents in December 1959, weighing 3120 g after a normal term pregnancy. She was breast-fed for 5 days and then given a full cream powdered milk preparation. From the early weeks the mother experienced difficulty in getting the child to take her feeds but she thrived initially.

Aged 3½ months. She weighed 4080 g. She then had an episode of diarrhoea lasting for 2 weeks and thereafter ceased to gain weight at a normal rate and the feeding difficulties intensified.

Aged 7½ months. She was referred to another hospital

weighing 4600 g (below the 3rd centile). Her stools were said to be intermittently loose and foul smelling, but there had been no vomiting. Cereals had been added to her diet from the age of 4 months. It was noted that she was lively and contented despite her marasmic appearance. The bone age was estimated at less than 6 months (no carpal ossification centres). Other investigations were normal including serum electrolytes, blood urea, sweat sodium, faecal tryptic activity, and x-rays of the chest and skull.

Aged 8 months. The child was admitted to Alder Hey Children's Hospital under the care of one of us (F.P.H.). She weighed 4930 g and her head circumference was 43.0 cm (below the 10th centile). The striking features on clinical examination were an extreme cachexia accompanied by a remarkable liveliness and pallor. There was no clinical evidence of raised intracranial pressure and systematic examination was otherwise normal.

Further investigations were normal and included blood count, faecal trypsin, fat balance (98% absorption), vitamin A and lactose absorption tests, urinary reducing substances, amino acids, 17-ketosteroids and 17-ketogenic steroids, and barium meal and follow-through.

A period on a gluten-free diet failed to produce a gain in weight and the child was sent back to the referring hospital aged 9 months weighing 4820 g.

Aged 12 months. She was seen by Professor D. Hubble at the Birmingham Children's Hospital when she weighed 4930 g and measured 66.0 cm (less than the 3rd centile). Investigations were again normal including serum protein-bound iodine, lipids, and lipoproteins. X-rays of skull were again normal and the bone age remained at about 3 months.

A diagnosis of 'functional' hypothalamic disturbance was made. Hypothalamic tumour was considered a possibility but further investigation at that stage was not felt to be justifiable.

Aged 20 months. Seen at follow-up by the original referring paediatrician (Dr. T. E. D. Beavan) she had begun to vomit. The head had a hydrocephalic appearance with a 'cracked pot' percussion note and a circumference of 49.5 cm (above the 50th centile). There was bilateral papilloedema and skull x-ray showed separation of the sutures. She developed a tremor of her right hand and rapidly progressive unsteadiness so that she was soon unable to walk.

Aged 21 months. She was transferred to the care of Mr. R. H. Hannah. Ethiodan ventriculogram showed considerable dilatation of both lateral ventricles but the contrast would not enter the 3rd ventricle. Following this procedure the child's condition deteriorated and she died aged 22 months.

Necropsy findings. (Dr. P. Buxton) A firm tumour mass presented in the midline between the posterior edge of the chiasm and the third nerve origin. The chiasm was pushed right forward so that the optic nerves left the chiasm vertically. The arachnoid around the brainstem was more opaque than usual.

When the cerebellum and brainstem were removed by cutting through the aqueduct and peduncles the suprapineal recess was grossly expanded leaving a thin layer of ependyma separating it from the inferomedial aspects of the lateral ventricles. The tumour extended right back to this level and the mammillary bodies were completely replaced by the smooth tumour wall.

On gross section the tumour lay in the midline completely obliterating the third ventricle. It was firm, pale yellow speckled red, and measured $4 \times 3 \times 4$ cm. It appeared encapsulated at its upper and lower extremity but ran diffusely into the internal capsule and basal ganglia. The lateral ventricles and temporal horns were grossly dilated. Microscopy showed the tumour to be a glioma.

Case 3. A girl born of healthy parents in March 1965, weighing 2750 g, after a normal term pregnancy. Mild neonatal jaundice did not cause any concern. The mother had had 3 previous pregnancies: the first child, a girl, died of pneumonia aged 10 months, the second pregnancy ended in abortion at 2½ months, the third went to term but the child had spina bifida and hydrocephalus and was stillborn.

Aged 5 months. She developed a rotatory nystagmus at first only in the left eye, but after 2 weeks in both. She was otherwise well and when seen at Alder Hey Children's Hospital (Dr. S. E. Keidan) aged 6½ months she weighed 8220 g (97th centile). The fundi were normal and there was no other abnormality. The head circumference was 43.0 cm (just above the 10th centile). Motor and social development were normal.

Aged 7 months. She was admitted to Alder Hey Children's Hospital under the care of Dr. R. W. Smithells with a 12-day history of persistent vomiting. There had been no diarrhoea and cereals had been introduced into her diet without difficulty at the age of 5 weeks. On admission she weighed 7660 g and 3 weeks later 7060 g. She was noted to be lively and active and smiled readily. She was able to sit unsupported and played with toys, transferring objects from hand to hand. The head circumference was now 44.5 cm but the fontanelle was not tense and the fundi were normal. The nystagmus persisted but there was still no other abnormality on neurological examination.

Investigations. Blood count, blood urea and serum electrolytes, serum calcium, urine microscopy and culture, urine amino acids, and faecal culture were all normal. X-ray of skull was normal, and barium meal showed free gastro-oesophageal reflux but no hiatus hernia and no other abnormality.

On nursing upright in an 'oesophageal chair' she stopped vomiting and was allowed home to be seen again in the outpatient department.

Aged 9 months. She was refusing feeds and now weighed 6350 g (less than the 3rd centile). The physical signs were unchanged. The CSF protein was 160 mg/100 ml and an air encephalogram (Dr. J. V. Occle-

shaw) showed dilated lateral ventricles and a large tumour mass indenting the floor of the 3rd ventricle.

The child was then transferred to the care of Mr. A. G. MacIntyre at Walton Hospital Neurosurgical Unit, who aspirated 10 ml of golden yellow fluid from the area of the lesion. The probable diagnosis was thought to be either craniopharyngioma or astrocytoma but the risks of operative interference were felt to be prohibitive.

Aged 10 months to 2 years. She was followed up in the outpatient department. Her nystagmus became much less marked and her appetite improved. Her weight increased from 6350 g to 9100 g and her head circumference from 45.0 cm (just above the 10th centile) to 52.0 cm (90th centile). Her speech developed normally and at 19 months she was walking with support. Her vision was thought to be imperfect and the optic discs were pale but she would reach accurately for small objects.

Aged 2 years. She was again admitted because of lassitude, anorexia, and vomiting. Repeated aspiration of the cyst and drainage of the lateral ventricle was carried out in the Neurosurgical Unit but she rapidly deteriorated and died at the age of 2 years 1 month.

Necropsy findings. (Dr. P. Buxton.) There was a large central tumour mass 6 cm in diameter, which appeared to be attached to the posterior end of the third ventricle. Elsewhere, though the tumour produced extensive displacement of brain structures, there appeared to be no actual invasion. The whole of the central grey matter apart from the peripheral edge of the putamen was replaced by tumour.

Microscopy showed a well-differentiated astrocytoma of juvenile microcystic alveolar type.

The pituitary gland showed a small area of infarction in the anterior lobe.

Analysis of Literature

Russell (1951) in describing 5 patients listed the clinical features of the syndrome as follows:

Major features—emaciation, initial growth acceleration, locomotor overactivity, and euphoria.

Minor features—pallor without anaemia, hypoglycaemia, and hypotension.

The last two of these features have not been recorded by other authors.

What follows is an analysis of 45 cases from the English, French, and German literature together with our own three (Table).

TABLE

Sex (47 cases): 30 boys, 17 girls	
Birthweight (33 cases): mean 3340 g, range 2330–4500 g	
Age at onset of first symptoms:	
< 6 months	28 (15 boys; 13 girls)
6–12 months	16 (12 boys; 3 girls) (1 sex not given)
12–24 months	2 (1 boy; 1 girl)
> 2 years	2 (boys)
Age range at onset 1 week–3 years	

Weight at presentation (39 cases)		
<3rd centile	29	
3–10th centile	3	
10–50th centile	6	
> 50th centile	1	
Height at presentation (25 cases)		
> 90th centile	8	
50–90th centile	8	
10–50th centile	4	
3–10th centile	2	
<3rd centile	1	
'normal'	2	
Appetite at onset of illness (34 cases)		
Poor 14, normal 16, excessive 4		
Vomiting at early stage (44 cases)		
Present 23, absent 21		
Diarrhoea at early stage (40 cases)		
Present 7, absent 33		
Hyperactivity (40 cases)		
Present 33, absent 7		
Pleasant disposition or euphoria (38 cases)		
Present 29, absent 9		
Pallor without anaemia		
Present 25, not mentioned 23		
Nystagmus (45 cases)		
Early 25, late 2, absent 18		
Optic fundi (39 cases)		
Normal	20	
Optic atrophy at first examination	11	
Normal at first—optic atrophy later	5	
Papilloedema at first examination	1	
Normal at first—papilloedema later	2	
Fontanelle		
In no patient was increased fontanelle tension noted at presentation		
Head circumference at presentation (27 cases)		
> 90th centile	2	
10th–90th centile	12	
< 10th centile	13	
Other CNS findings		
All occurred late in the course of the illness		
Tremor	8	
Ataxia	5	
Hyperreflexia	4	
Hemiparesis	3	
Homonymous hemianopia	3	
Squint	3	
Hypotonia	3	
VIth nerve palsy	2	
Athetoid movements	2	
Anisocoria	1	
Ptoxis	1	
Facial weakness	1	
CSF protein (31 cases)		
'Normal CSF'—protein not specifically mentioned	7	
Protein initially < 40 mg/100 ml and later > 100	2	
Protein < 40 (one examination only)	5	
Protein > 40 at first examination	17	
Protein > 100 at first examination	12	
Bone age (17 cases)		
Normal	14	
Advanced	1	
Retarded	2	
Other clinical features occasionally recorded		
Excess sweating (5 cases)		
Large hands and feet (2 cases)		
Large genitalia		
Heat intolerance		
Poor temperature control		
Loose skin		
Eosinophilia		
Hyperchloraemia or hypochloraemia		
Convulsions only occurred terminally		

Lid retraction (Collier's sign of an upper brainstem lesion) was not commented on by any of the authors but Snyder (1965) pointed out that several of the published photographs appear to show this sign

Pathology. In almost all cases a tumour involving the diencephalon and arising from either the floor of the third ventricle or the optic chiasm has been found. Atypical findings have been described, however. Dods (1957, 1967) reported the case of a child with the typical clinical features of the diencephalic syndrome who was alive and well 9 years after the removal of a midline astrocytoma of the medulla oblongata. One of the children described by White and Ross (1963) had an astrocytoma which originated in the posterior fossa and spread to the middle fossa, and Bain *et al.* (1966) described a typical AEG findings in one of their patients who showed a filling defect in the right lateral ventricle thought to be caused by a tumour of the thalamus.

Histologically the tumours have most commonly been astrocytomas. The findings in the 48 cases were as follows:

Astrocytoma, 23; 'glioma', 6; spongioblastoma, 4; ependymoma, 2; oligodendroglioma, 1; astrocytoma/spongioblastoma, 1; astrocytoma/oligodendroglioma, 1; astroblastoma, 1; no biopsy, 8; and histology uncertain, 1.

Outcome. Complete operative removal of the tumour was never possible.

23 patients were given radiotherapy; 2 died 6 months and 18 months after treatment; 2 were not followed-up; 19 were alive at follow-up of whom 6 had survived for over 2 years after treatment, 5 had survived for 13 to 24 months, 6 had survived for 6 to 12 months, and 2 had survived for less than 6 months.

25 patients were not given radiotherapy; 22 were dead at the time of reporting; 1 was alive but deteriorating about 8 months after the onset; and 2 were not followed up.

Time from onset to death in 22 untreated patients: less than 6 months, 5; 7–12 months, 9; 13–24 months, 4; over 2 years, 3; and not known, 1.

No correlation was found between age at onset or interval between onset and treatment and outcome.

Discussion

When considering the relative frequency of the many causes of failure to thrive, a diencephalic tumour comes low on the list. The diagnosis is seldom contemplated until more common causes of wasting have been excluded. In contrast to most other brain tumours of early life this variety is slow

to disclose its presence by positive neurological signs.

Three major features of the syndrome were emphasized in Russell's description, and their importance has been amply confirmed in subsequent reports. They are emaciation, seemingly incongruous overactivity and pleasantness, occasionally amounting to euphoria, and initial growth acceleration. Signs of autonomic disturbance may include skin pallor, profuse sweating, erratic temperature control, and heat intolerance. Nystagmus, usually rotatory, and possibly lid retraction, are the only other neurological signs which may occur early. Evidence of increased intracranial pressure may not be found until many months after the initial presentation. Investigations at an early stage are usually unhelpful. Several authors have commented on the complete absence of subcutaneous fat on soft tissue films of the limbs, and this may help to distinguish this syndrome from other causes of emaciation where a thin fat line is usually retained (Poznanski and Manson, 1963; Smith, Weinburg, and McAlister, 1965; Girdwood and Ross, 1969). CSF protein may be raised, but early in the disease will often be normal. Confirmation of the diagnosis requires neuroradiological investigation.

The natural course of the disease is varied. Most untreated patients die 6 months to 2 years after the onset, but Goebel (1932) and Weller (1951) described patients surviving untreated for 2 years 10 months and 4 years, respectively. Bain *et al.* (1966) quote a personal communication from Russell relating his experience of 16 cases seen over a period of 12 years; 2 of his untreated patients were alive after 8 years and 11 years, and 1 patient was alive 12 years after a Torkildsen procedure only. Of 23 patients documented as being treated by radiotherapy, 19 were alive at follow-up from 3 months to 9 years later, 2 were not followed-up, and 2 died 6 months and 18 months after treatment. 11 survivors were followed up for over 12 months after radiotherapy and 6 for over 2 years. Russell again has the last word; he tells of one patient who was well for 4 years after radiotherapy but died 1 year later despite further treatment (A. Russell, personal communication to Bain *et al.*, 1966).

The value of exploratory operation is doubtful. 7 of the 48 patients included in our analysis died within 6 weeks of such an operation. Two patients died soon after air encephalogram and one of our own died 3 weeks after Ethiodan ventriculogram. Admittedly the patients might have died equally quickly without these procedures, but we have an

impression from the literature that intervention may on occasions be the last straw. Complete removal of the tumour has never been found practicable, and biopsy is only of academic interest having no influence on treatment. Radiotherapy offers the most hope and should probably follow closely upon radiological confirmation of the diagnosis. Aspiration of a cystic lesion, as in our third case, may give prolonged relief of symptoms, and a CSF shunt operation may be necessary because of blockage at third ventricle level.

The cause of emaciation in the diencephalic syndrome remains unknown. Lesions of the lateral hypothalamic nuclei in animals cause emaciation by producing anorexia, but it is amply documented that children with a diencephalic tumour fail to thrive despite a known adequate food intake. It has been suggested that the emaciation might be due to excess metabolic expenditure coincident on the hyperkinesia, but this feature is not always present and the degree of fat depletion seems excessive for this explanation. Increased mobilization of fat from the tissues is an attractive hypothesis, especially in view of the finding of increased serum levels of growth hormone by several authors (Smith *et al.*, 1965; Pimstone *et al.*, 1970; Fishman and Peake, 1970), but abnormalities of serum lipids have not been found in this syndrome, whereas in generalized lipodystrophy, another syndrome of probable hypothalamic origin, such serum abnormalities are known to occur (Ruvalcaba, Samols, and Kelley, 1965; Seip, 1959).

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