Cerebral oedema with coning in diabetic keto-acidosis

Report of 2 survivors

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Summary

Two children presented with a first episode of diabetic keto-acidosis. Initially both patients made a good clinical and biochemical recovery, but suddenly developed neurological signs consistent with a diagnosis of tentorial herniation. Cranial computed tomography showed signs of cerebral oedema in both cases with evidence of uncal and tentorial herniation in 1 patient, which resolved after the appropriate treatment. The excellent neurological outcome emphasises the need for early recognition and treatment of sudden onset brain oedema in diabetic keto-acidosis.

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Cerebral oedema and coning may develop unpredictably during the treatment of diabetic keto-acidosis. The outcome is usually fatal and only a few reports of successful medical management are available. Two cases with clinical and neuroradiological evidence of cerebral coning and successful intervention are presented.

Case reports

Patient 1

A 7-year-old girl had a 2-month history of weight loss following an episode of mumps. One week before admission she developed polydypsia, polyuria, general malaise and weakness and complained of diarrhoea and abdominal pain. After a diagnosis of diabetic keto-acidosis was made at a peripheral hospital, the patient received 6 U of soluble insulin.

On admission to Tygerberg Hospital the patient was afebrile but severely dehydrated and ketotic. The blood pressure was $^{115}/_{75}$ mmHg and the pulse rate 120/min. Systemic examination was normal. The urine contained 2^+ glucose, 4^+ ketones and was normal on microscopy. Results of chemical and haematology tests on admission are shown in Table I.

An intravenous infusion of 0,9% NaCl was started, 25 ml/kg for the first hour, followed by 20 ml/kg for the following two hours. Thereafter 0,45% NaCl was administered at 55 ml/kg/24 h. Soluble insulin was administered as a constant infusion at a dose of 0,05 - 0,1 U/kg/h.

Potassium supplementation was added according to the electrolyte profile, initially as potassium phosphate and after 8 hours as 15% potassium chloride. As a constant infusion 30 ml 4,2% $NaHCO_3$ was infused slowly over 6 hours. Broad-spectrum antibiotic cover was administered.

Clinical course

Ten hours after admission to hospital the patient suddenly became deeply comatose and decerebrate. The left pupil dilated acutely and became unresponsive to light. Bilateral papilloedema was present and no brainstem responses could be elicited. A clinical diagnosis of acute cerebral oedema and coning was made.

The patient was intubated and hyperventilated. Cerebral oedema was managed with fluid restriction (only insensible loss replaced), intravenous infusion of mannitol in a dose of 0,25 g/kg, dexamethasone (2 mg/kg), and phenobarbitone (10 mg/kg loading dose). Computed tomography (CT) (Fig. 1) demonstrated generalised cerebral swelling with evidence of uncal and tentorial herniation.

One hour after the onset of therapy, the patient became responsive to pain and both pupils reacted to light. Twenty-four hours later the patient had purposeful responses to pain and responded to simple commands. She was extubated after 2 days and started on oral feeds. Short-acting insulin was administered according to blood glucose levels. She continued to show aggressive tendencies and inappropriate behaviour. Further recovery was rapid and uneventful and the patient was discharged after 30 days with no short-term neurological sequelae.

Six weeks after discharge repeat CT showed normal-sized ventricles (Fig. 2) and subarachnoid spaces, but an infarct of the left occipital lobe. At present the patient is leading a normal life and is a top performer in school.

TABLE I. RESULTS OF THE INITIAL CHEMICAL AND HAEMATOLOGY TESTS CARRIED OUT

Tests	Case 1	Case 2
Blood		
pH	7,00	7,14
Carbon dioxide content	4,9	5,0
Partial arterial carbon dioxide pressure (kPa)	3,3	4,4
Base excess	−26	−22
Glucose (mmol/l)	23	26
Serum		
Na^+ (mmol/l)	127	136
Cl^- (mmol/l)	112	108
K^+ (mmol/l)	4,3	5,0
Urea (mmol/l)	4,2	8,9
Osmolality	310	326
Haematology		
Haemoglobin (g/dl)	12	12
White cell count ($\times 10^9$/l)	6 800	16 000

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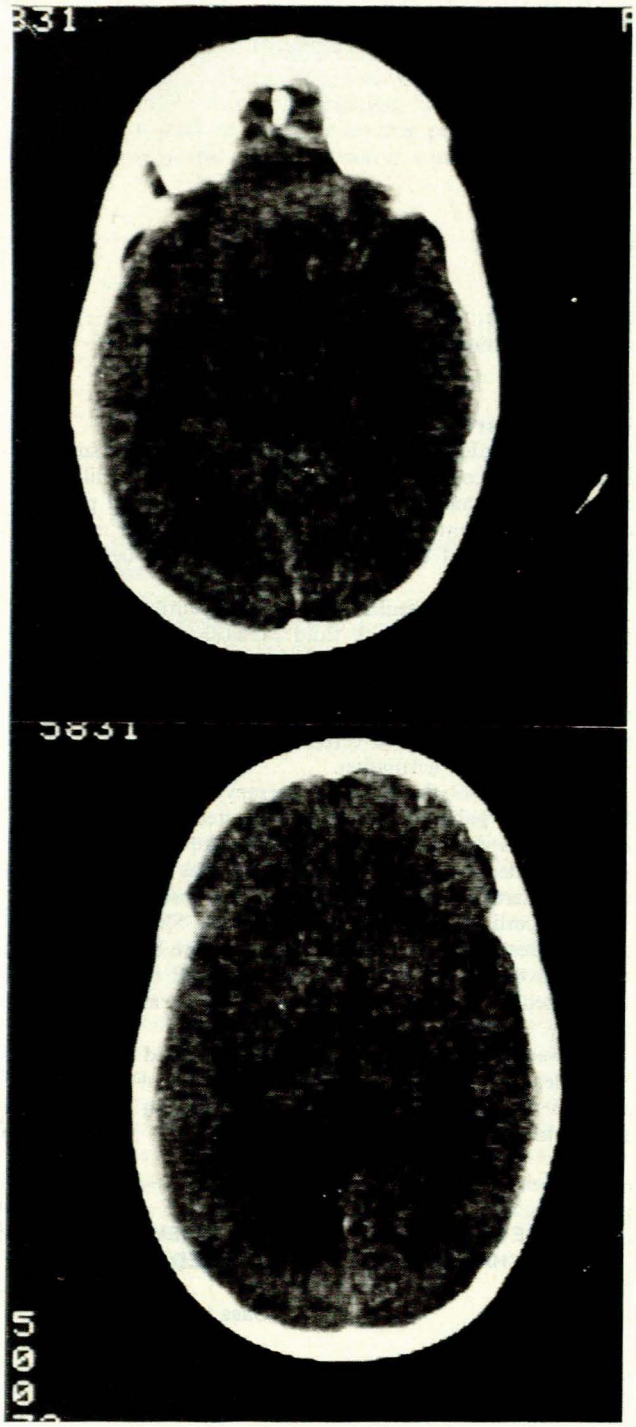

Fig. 1. CT without contrast medium, demonstrating generalised loss of grey-white differentiation, sulcal effacement and effacement of the left ambient cistern with evidence of uncal and transtentorial herniation.

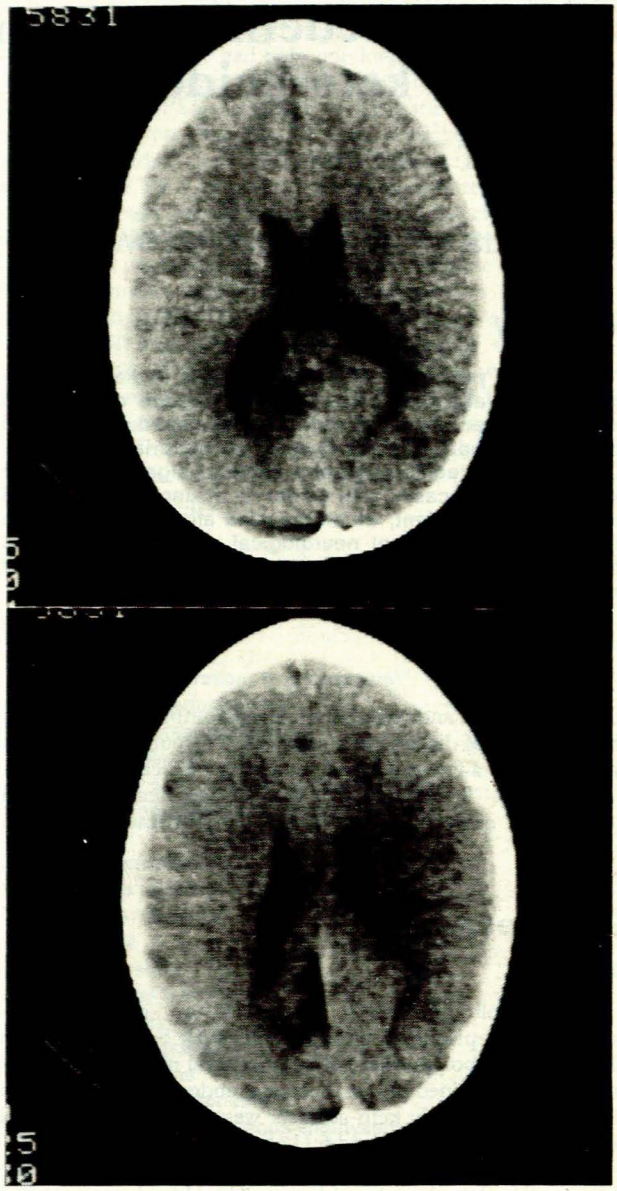

Fig. 2. CT without contrast medium, demonstrating return of grey-white differentiation and return of lateral ventricular size to normal limits (above). CT without contrast medium, demonstrating focal atrophy in the left occipital lobe corresponding with the resolving gliomesodermal response and spongiosis of the posterior cerebral infarct (below).

Patient 2

An 11-year-old girl was admitted to Tygerberg Hospital with an acute first episode of diabetic keto-acidosis after a 4-week history of apathy, poor appetite, polyuria and polydypsia.

On examination she was acutely ill but fully conscious. The blood pressure was 125/80 mmHg, and the pulse rate 135/min. The rest of the clinical examination appeared normal and no focus of infection could be located. Results of initial chemical and haematology tests are shown in Table I.

Management consisted of intravenous infusion of 0,9% NaCl 25 ml/kg during the first hour, followed by 20 ml/kg for the following two hours. Soluble insulin was administered as a constant infusion of 0,06 U/kg/h, and K^+ supplemented as potassium phosphate initially and 15% potassium chloride after 6 hours. Initially, 30 ml of 4,2% $NaHCO_3$ was given as constant infusion over 6 hours. She received broad-spectrum antibiotic cover.

Clinical course

Six hours after admission to hospital the patient suddenly became comatose with unreactive pupils, but no papilloedema was present. CT was compatible with diffuse cerebral oedema (Fig. 3).

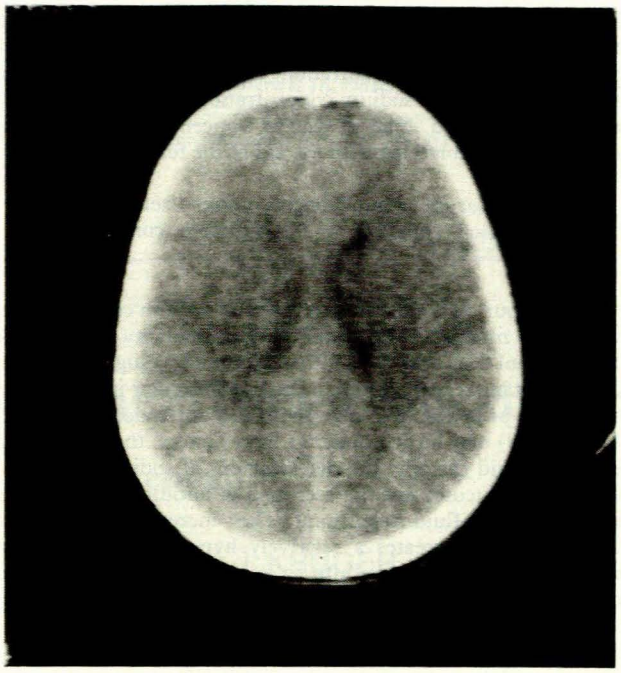

Fig. 3. Unenhanced CT of the brain demonstrating relative effacement of the ambient cisterns, small lateral ventricles and low density of the centrum semiovale compatible with cerebral swelling and oedema.

The patient was treated with fluid restriction (only insensible loss replaced), intravenous infusion of mannitol 0,25 g/kg, phenobarbitone 10 mg/kg, and dexamethasone. Due to a poor response to treatment, a second course of intravenous mannitol, 0,25 g/kg was given.

Thirty hours after the onset of treatment the patient reacted appropriately to pain, but showed signs of a left-sided hemiparesis. Emotionally, she was unstable and aggressive, and had episodes of severe depression and loss of short-term memory. There was also a persistent bradycardia at this stage. During the following days the patient gradually improved and by day 20 the gait had normalised without any evidence of a hemiparesis. The depression was treated with amitriptyline. Follow-up CT 3 weeks later showed complete resolution of the cerebral oedema, but an unexplained low-density area in the region of the right thalamus (Fig. 4). Magnetic resonance imaging (MRI) (Fig. 5) confirmed these findings.

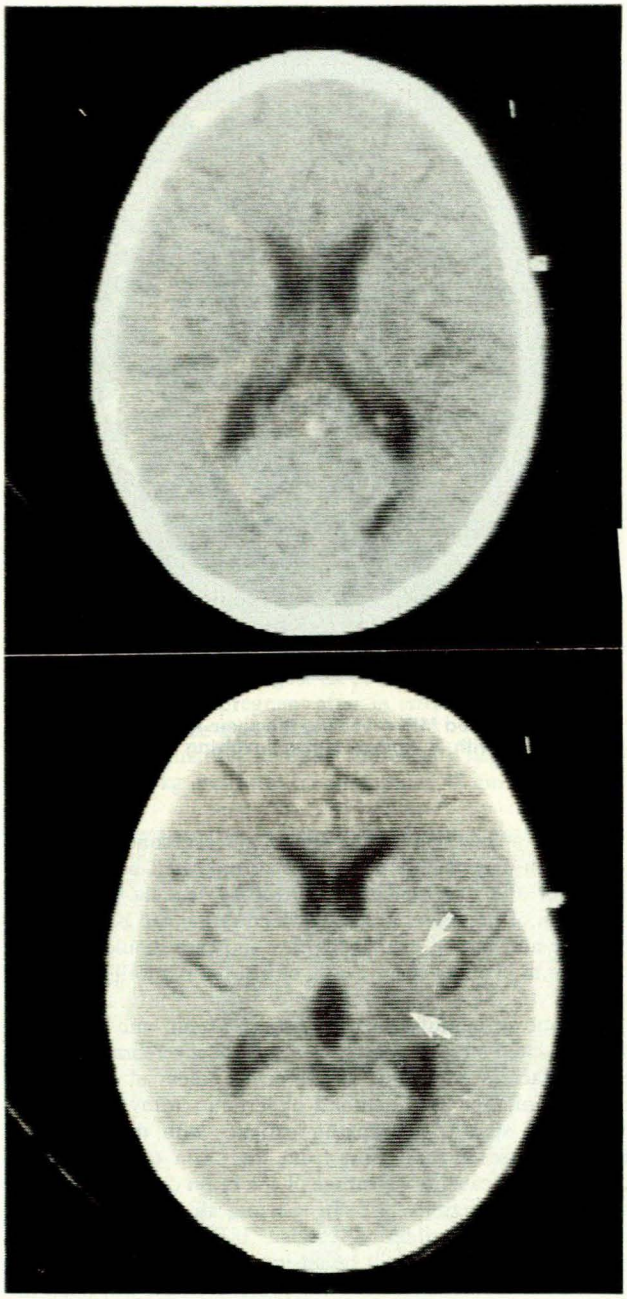

Fig. 4. Follow-up CT at 3 weeks demonstrating return to normal of the lateral ventricles, sulci and white matter (above). **CT demonstrating low densities in the right thalamus** (arrows) (below).

Discussion

Fatal cerebral oedema with herniation as a complication of diabetic keto-acidosis appears to be more common in childhood than in adults.[1-3] More than half the recorded cases occurred in newly diagnosed diabetics during their first episode of keto-acidosis.[4] The development of cerebral oedema is usually unsuspected until signs of herniation appear, as in the two patients presented here. Tentorial herniation due to cerebral oedema usually becomes evident 6 - 13 hours after the initiation of treatment, at a time when the patient appears to be recovering satisfactorily and the biochemical parameters seem to be improving.[4] The clinical signs are sudden deterioration of consciousness, absent brainstem responses and eventual respiratory arrest, such as was demonstrated in patient 1.

The pathophysiological mechanisms responsible for the development of cerebral oedema are not clear. It has been shown that cerebrospinal fluid pressure only rises after the onset of treatment, suggesting that the induction of therapy causes this elevation.[5]

Various hypotheses have been proposed as to the mechanisms responsible for the development of cerebral oedema. Some of these factors are: the rate of insulin therapy;[6] the rate of glucose reduction;[7] osmolar disequilibrium between the vascular and extravascular brain compartments;[7] integrity of the blood-brain barrier;[6] the rate, volume and tonicity of fluid therapy;[8] antidiuretic hormone secretion with resultant fluid retention;[9] the formation of 'idiogenic osmoles';[10] and the rate of acid-base correction with activation of the plasma membrane exchanger.[11]

The assumption that cerebral oedema does not develop when the blood glucose remains $>$ 200 mg/dl, is false.[7]

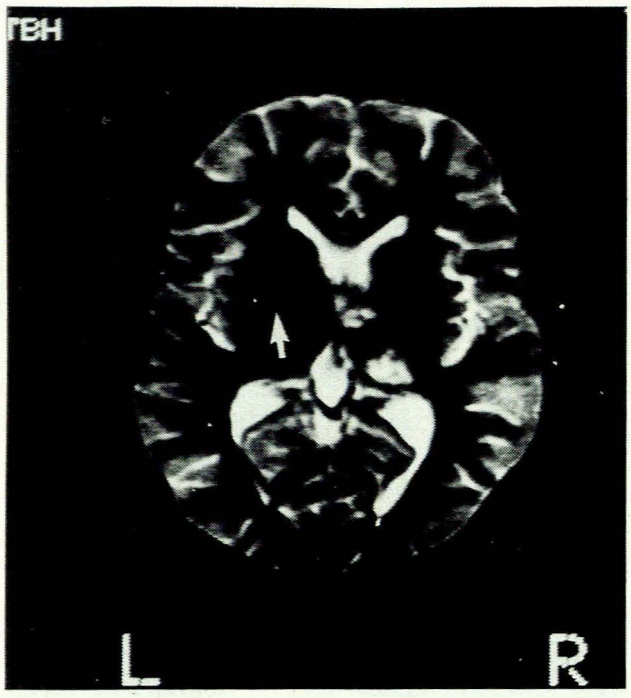

Fig. 5. T2 weighted MRI revealing the same hyperintense lesions on the right with a further lesion involving the left putamen (arrow).

However, a lowering of the blood glucose concentration of more than 100 mg/dl/h has been implicated as a possible cause for the development of cerebral oedema.[7] A sudden reduction of the blood glucose concentration can be related to the dose and rate of insulin therapy and care should therefore be taken to give the correct dose of insulin in a well-controlled way.

Osmotic disequilibrium between the brain and the blood has been cited most frequently as the cause of cerebral oedema.[12] Several factors contribute to the development of such a disequilibrium. The presence of a hypertonic intravascular state before the start of therapy in patients with diabetic keto-acidosis causes a fluid shift from the brain to the vascular compartment causing shrinkage of the brain cells and opening of the tight junctions, thereby causing an increased permeability of the cerebral blood vessels.[13] If fluid of low tonicity is given in excess, there will be an increase in the intravascular volume and hydrostatic pressure, which in turn will open the tight junctions even further, with subsequent loss of solutes, electrolytes and water into the extravascular space, thus causing cerebral oedema.[13] Although it has been recommended that fluid should not be given in excess of 4 l/m^2 of body surface area, many cases of cerebral oedema have been reported in patients who received less than this amount of fluid.[8] Patients have been reported to develop cerebral oedema after oral rehydration,[1,2,4] thus implicating other pathogenetic factors. One such factor could be the accumulation within the brain cells of 'idiogenic osmoles'. These are intracellular solutes generated through an integrated series of biochemical and enzymatic steps[10] and they are thought to prevent excessive shrinkage of the brain when the plasma is hypertonic.[5] Clements *et al.*[5] have suggested that correction of the hyperosmolar state in diabetic keto-acidosis allows these 'idiogenic osmoles' to draw free water into the brain cells because they dissipate slowly after serum osmolality has returned to normal.

Patients with an initial hyponatraemia (< 130 mmol/l) were found to be particularly at risk of developing cerebral oedema after treatment of diabetic keto-acidosis.[8] The presence of a low serum sodium concentration therefore does not imply a low serum osmolality because other substances, for example a high serum glucose concentration, may cause a hyperosmolar state.[14] A low serum sodium concentration, on the other hand, cannot be ignored. The measured concentration should be mathematically corrected with the aid of the following equation:

> calculated serum sodium concentration = serum sodium concentration (mmol/l + 0,5 {glucose concentration (mmol/l) − 5,5}[14]

In both our cases the calculated serum sodium concentration was < 150 mmol/l. Even so the serum osmolality in both was > 310 mmol/l (normal value 270-300 mmol/l) suggesting that other substances contributed to the hyperosmolar intravascular state. The presence of a low serum sodium concentration (< 130 mmol/l) may be attributed to three factors: the dilution by excessive fluid therapy; the displacement of sodium by excessive serum glucose; and the secretion of antidiuretic hormone with resultant fluid retention.[8] This increase in the total vascular volume creates a relatively hypotonic intravascular state with a free fluid shift to a relatively hyperosmolar extravascular compartment, causing cerebral oedema.

The role of concurrent rehydration and soluble insulin therapy remains unclear. The main criticism of the experimental models in rats is that no parallel experiments on the effects of insulin therapy alone without concomitant rehydration have been performed. The high intracellular potassium levels in the presence of cerebral oedema raise the possibility that insulin could drive K^+ ions intracellularly, with water following the osmotic gradient.

Sodium bicarbonate therapy for metabolic acidosis results in cerebrospinal fluid acidosis and a lowered cerebrospinal fluid carbon dioxide pressure with secondary hypoxia and shift of the oxygen dissociation curve to the left. This effect is accentuated by the depressed levels of 2,3-diphosphoglycerate in diabetic keto-acidosis. The possibility therefore exists that the development of cerebral oedema is secondary to initial cerebral hypoxia.

The life-threatening brain oedema that occurred in our patients cannot be ascribed to a particular cause with certainty. These 2 cases, however, illustrate the importance of meticulous monitoring of the neurological state of children with diabetic keto-acidosis in order to diagnose impending tentorial herniation at an early stage. We have furthermore shown that prompt treatment of cerebral oedema in this condition can reverse the situation. Neuro-imaging confirmed the clinical diagnosis of massive brain oedema with uncal and tentorial herniation (patient 1), which resolved after the appropriate treatment was given. The excellent neurological outcome in our patients was encouraging and underlines the importance of early recognition and treatment of brain oedema in diabetic keto-acidosis.

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Turner/Down mosaicism

A case report

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Summary

A 45,X/47,XX, +21 mosaicism (80%:20%) in a young girl with clinical features of Down syndrome is reported. The proportion of 45,X:47,XX, +21 cells present in peripheral lymphocytes does not necessarily have a profound effect on the phenotype. A possible explanation for the occurrence of double aneuploidy is given.

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Double aneuploidy has been reported in several combinations, including Down/Klinefelter, Down/XXX[1] and Turner/Patau syndromes.[2] The Down/Klinefelter combination is the most frequent double aneuploidy recognised.[3]

Turner/Down mosaicism usually occurs as a phenotypical Down syndrome with cytogenetic mosaicism of different varieties.[4] The clinical features and cytogenetic findings in a patient with this condition are described in order to delineate this entity further, in particular with regard to morphological features in relation to cytogenetic findings.

Case report

An 8-year-old girl attending a school for the mentally handicapped, with clinical features of Down syndrome was referred for cytogenetic analysis to confirm the diagnosis.

The proband was the first child of unrelated parents and was born after an uneventful pregnancy. The mother was 24 years and the father 26 years of age at the time of her birth. Neither parent has any family history of Down or Turner syndromes.

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The mother later gave birth to a normal boy. This was followed by two miscarriages. At present the mother, aged 32 years, is 12½ weeks pregnant after *in vitro* fertilisation, infertility having become a problem.

Clinical examination revealed the child's height to be 109 cm, weight 18 kg and head circumference 48 cm. Craniofacial

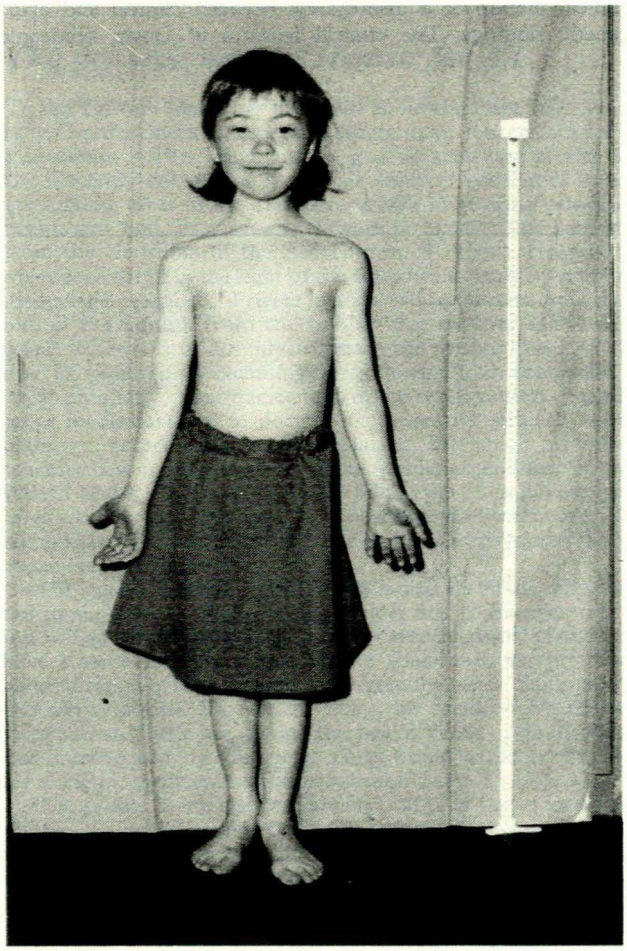

Fig. 1. The proband, aged 8 years.