Failure to thrive in children

When the cause is due to hormones

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Assessment of failure to thrive (FTT) in children can be challenging and early consultation with a general paediatrician is counselled. Although endocrine causes are rare, the consequences of missing them can be life-threatening and they are relatively easily excluded. This article presents a series of cases and screening investigations to help direct investigation or appropriate referral for different endocrine disorders that may present as FTT.

Key points

- **Failure to thrive describes poor weight gain with preserved linear growth, although linear growth failure will follow in time.**
- **Most endocrine causes of failure to thrive are uncommon but important to consider and screen for.**
- **The key to excluding endocrine causes is to think of them.**

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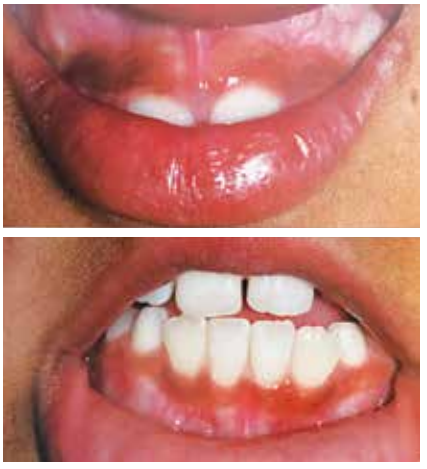
Failure to thrive (FTT) is a description rather than a diagnosis,[1,2] referring to poor weight gain resulting in the downward crossing of percentiles associated with a relative sparing of linear growth. In infancy, this is not necessarily pathological and may represent either reversion to the mean of a big baby or catch-down to genetic potential. Although organic or psychosocial pathology is identified in fewer than 85% of cases of FTT,[2] it needs to be excluded, particularly when poor weight gain is prolonged (e.g. more than six to 12 weeks in an infant) and/or out of keeping with the family background.

Initial assessment

In the first instance, assessment of a child with FTT should include the gathering of past growth data, including birth parameters, parental and sibling stature and growth history, and careful evaluation of the child's nutritional intake and psychosocial wellbeing. Accurate measurement of the child's length or height, weight and head circumference using a reproducible technique is important for comparison. Measurements should be plotted on appropriate growth charts and corrected for significant prematurity (i.e. if the baby is more than four weeks premature, subtract the number of weeks of prematurity from the postnatal age when plotting growth parameters in the first two years of life). The infant's nappy should be removed because it makes the weight unreliable and interferes with accurate measurement of supine length. Supine lengths are used until the child will reliably stand for a measurement and hence growth charts are based on lengths up to 3 years of age. Supine length exceeds standing height by up to 0.7 cm.

The period of observation before initiating paediatrician referral depends on the presence of other red flags such as:

- rapid unexplained weight loss
- irritability
- vomiting
- symptoms suggestive of hypoglycaemia (e.g. lethargy, pallor,



Figures 1a to c. Skin and mucous membrane hyperpigmentation in a 12-year-old girl with primary adrenal insufficiency (Addison's disease). Note the hyperpigmentation over the knuckles and patches of hyperpigmentation on the skin of her arms, some of which are attributable to scars.

sweating, not waking for feeds)
- polyuria (frequent soaked nappies or secondary enuresis in an older child) and polydipsia (increased drinking through the day or overnight and a preference for water)
- abnormal examination findings such as decreased subcutaneous fat (saggy buttocks), hyperpigmentation of skin or gums, dysmorphism, neurological abnormality or hepatomegaly, developmental delay or suspicion of abuse or neglect.

Prolonged failure to gain weight will eventually lead to failure of linear growth, especially in infants. If linear growth crosses percentiles at the same time as weight, so that the child's weight for height is preserved, this might represent either catch-down to genetic potential or point to a problem with linear growth for which endocrine aetiologies need to be excluded.

Causes of FTT

The possible causes of FTT can be categorised as the following:
- inadequate nutrient intake
- excessive nutrient loss
- metabolic requirements exceeding intake creating a net catabolic state.

By far the most common cause of FTT is inadequate nutrient intake. An endocrine aetiology for FTT is rare, even in a selected population of children with FTT referred to a paediatric endocrinology clinic. As shown in the case presentations, common findings associated with FTT are the irritable baby who feeds poorly and vomits, which are certainly not specific for an endocrine cause.

Once FTT is established in the primary care setting, early discussion with or referral to a paediatrician is suggested. Given the many caveats to endocrine investigations and their interpretation, early discussion with a paediatric endocrinologist for suspected hormonal causes of FTT may be beneficial.

The major endocrine disorders that may be associated with FTT and screening investigations for them are discussed below.

FTT associated with inadequate intake

Adrenal insufficiency

Children with adrenal insufficiency tend to be prone to more severe and prolonged trivial illnesses than other members of their family. They have poor appetite and poor weight gain or even weight loss, but preserved linear growth. Adrenal insufficiency can be primary (i.e. the problem lies in the adrenal glands), associated with impaired ability of the adrenal glands to respond to adrenocorticotrophic hormone (ACTH), or secondary (i.e. the problem lies in the pituitary gland or hypothalamus), associated with ACTH deficiency. Secondary adrenal insufficiency is associated with glucocorticoid (cortisol) but not mineralocorticoid deficiency, because aldosterone production is independent of ACTH.

Irrespective of whether the adrenal insufficiency is primary or secondary, glucocorticoid deficiency is associated with a risk of hypoglycaemia (blood glucose level [BGL] below 3 mmol/L). In the absence of a documented low BGL, there may be a suggestive history of lethargy, not waking for feeds, pallor or sweating.

The clinical and biochemical manifestations of primary and secondary adrenal insufficiency also differ. Hyperpigmentation of non-sun-exposed areas of the skin, gum mucosa, skin creases and scars is a hallmark of primary adrenal insufficiency (PAI), as shown in Figures 1a to c. Hyponatraemia and potentially life-threatening hyperkalaemia are features of PAI, whereas the hyponatraemia of secondary adrenal insufficiency (SAI) is usually mild and plasma concentrations of potassium remain normal. SAI is very rarely isolated and the clinical and biochemical manifestations will also reflect deficiencies of other pituitary hormones (see 'Pituitary insufficiency' below).

FTT is a prominent feature of isolated mineralocorticoid deficiency (hypoaldosteronism; Case 1) or, more often, aldosterone resistance (pseudohypoaldosteronism). It may also be associated with several monogenic, autoimmune and syndromic causes of PAI, but other presentations tend to predominate in these cases.[2] This is illustrated by the most common cause of PAI in childhood, congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency (autosomal recessive *CYP21A2* mutations; incidence one in 10,000 to 20,000), an enzyme crucial for cortisol and aldosterone synthesis.[3] In the most severe form of CAH with less than 2% residual 21-hydroxylase activity causing severe glucocorticoid and mineralocorticoid deficiency, girls are usually diagnosed soon after birth because of the associated virilised

Case 1. Adrenal insufficiency

Presentation

Douglas presented at 2 months of age for investigation of failure to regain his birth weight. His linear growth was also poor. He was lethargic and not particularly interested in feeds. He was from an olive-skinned background but was not hyperpigmented in skin creases. He had normal male genitalia.

Investigations

Douglas's electrolytes were suggestive of mineralocorticoid deficiency: plasma sodium concentration 119 mmol/L (reference range [RR], 130 to 140 mmol/L); potassium 7.3 mmol/L (RR, 3.5 to 5.5 mmol/L).

At this age, the most likely diagnosis would be a urinary tract infection usually with a structural renal tract anomaly causing transient distal renal tubular resistance to aldosterone; however, this was excluded on microurine analysis and ultrasound.

Congenital adrenal hyperplasia (CAH) associated with mineralocorticoid and glucocorticoid deficiency (*CYP21A2* deficiency) would be less likely because most babies with this degree of salt wasting would have presented in the first two to three weeks of life with cardiovascular collapse rather than FTT.

Accordingly, Douglas had normal concentrations of adrenocorticotrophic hormone (high/normal in CAH), 17-hydroxyprogesterone (high in CAH) and cortisol (low/normal in CAH); however, serum aldosterone concentrations were low. Genetic testing confirmed the rare diagnosis of aldosterone synthase deficiency.

Treatment

Douglas responded well to mineralocorticoid replacement (fludrocortisone) and salt.

genitalia. Diagnosis in boys is likely to be missed at birth; they will present with poor feeding, vomiting, lethargy, FTT, hyperpigmentation and various degrees of cardiovascular collapse due to adrenal crisis in the first two to three weeks of life. Milder degrees of deficiency present with early virilisation in infancy or early childhood (2 to 5% residual activity), or, in the late-onset form, with early pubic hair or acne in late childhood, or amenorrhoea in adolescent girls. Newborn screening for *CYP21A2* deficiency was recently introduced in Australia, with the hope of reducing morbidity and mortality by early diagnosis.

Investigations to screen for suspected PAI and SAI are listed in Box 1.

1. Diagnostic screen for suspected primary or secondary adrenal insufficiency

- Electrolytes, urea and creatinine levels
- Venous or capillary (finger prick) glucose level
- Paired adrenocorticotrophic hormone (ACTH) and cortisol levels (lab reference ranges are for 8 am sample)*
- 17-hydroxyprogesterone, renin and aldosterone levels

* In primary adrenal insufficiency, the cortisol concentration is usually inappropriately low for the ACTH concentration at any time of the day.

Hypopituitarism

FTT is a common association of undiagnosed congenital hypopituitarism. Because postnatal growth in the first six months of life is largely independent of growth hormone (GH), failure to gain weight may precede failure of linear growth even in infants with growth hormone deficiency. Birth parameters and gestational age are usually normal in affected infants, although there is an association with prolonged gestation and breech presentation.

The infant with hypopituitarism may be less active and not wake for feeds. The first few days of life may be marked by a history of apnoea, episodes of pallor or cyanosis, poor feeding and jitteriness, and nonspecific symptoms of hypoglycaemia that are sometimes mistaken (and treated) as sepsis. Prolonged conjugated or unconjugated jaundice in neonates is common (Case 2); however, liver impairment is fully reversible if pituitary hormone replacement is initiated in infancy.[5] In male infants, micropenis offers a clue to the diagnosis. Some infants have temperature instability. Septo-optic dysplasia is associated with congenital hypopituitarism in 50% of cases,[6] and this may be associated with congenital nystagmus and visual impairment.

Early diagnosis and hormone replacement with GH, hydrocortisone and levothyroxine are crucial to avoid the deleterious effects on neurological development of hypoglycaemia and hypothyroidism.

Acquired causes of hypopituitarism that may present with FTT include suprasellar tumours such as craniopharyngioma, astrocytoma and dysgerminoma, and infiltrative causes such as Langerhans cell histiocytosis. The latter, in particular, may present with diabetes insipidus (see below).

Investigations to screen for suspected hypopituitarism are listed in Box 2. The length and weight charts of a girl diagnosed with hypopituitarism at age 2 years and 7 months are shown in Figures 2a and b.

Diabetes insipidus

Diabetes insipidus (DI) is caused by either inadequate vasopressin secretion by the posterior pituitary (central DI) or impaired action in the renal distal convoluted tubule (nephrogenic DI; see Case 3). Central DI can be isolated or associated with multiple pituitary deficiencies, trauma or an infiltrative or destructive process (the most common cause in childhood), or it may be genetic (autosomal dominant). Autosomal dominant central DI usually only starts to manifest in the second or third year of life. Congenital nephrogenic DI is usually X-linked but there are also autosomal recessive and (more rarely) dominant forms.

Irrespective of the cause and type, DI results in obligatory urinary water loss and, as a consequence, increased thirst. Affected individuals have a strong preference for iced water. In hereditary forms, there may be a family history of storing litres of water in the refrigerator or taking many bottles on family outings. The affected child will have a history of frequent soaked and overflowing nappies or primary or secondary enuresis. A mobile

Case 2. Hypopituitarism

Presentation

Edward was born breech at 37 weeks' gestation with a birth weight of 2.8 kg (25 to 50th percentile). He became hypoglycaemic within 12 hours of birth, needing intravenous dextrose for four days. He developed jaundice on day two, which persisted, and needed readmission at 1 week of age and again at 13 days of age for phototherapy. His thyroid stimulating hormone (TSH) level was normal and free thyroxine (FT4) not checked. Persistence of jaundice was attributed to breast milk jaundice.

He re-presented for medical review twice with drowsiness and poor feeding and was described by his mother as an undemanding baby who hardly ever cried. At 15 weeks of age he was still jaundiced and failing to thrive, with length and weight below the 3rd percentile (worse for weight).

Investigations

Investigations showed Edward had conjugated jaundice with cholestatic liver dysfunction, warranting urgent investigation for biliary atresia. Bedside blood glucose level (BGL) testing showed hypoglycaemia prior to three-hourly feeds. Blood collected when his BGL was 2.3 mmol/L showed a growth hormone (GH) level of 0.6 mcg/L and cortisol level of 45 nmol/L, both inappropriately low. Thyroid function tests were consistent with central hypothyroidism with a TSH level of 5.4 mIU/L (reference range [RR], 0.73 to 8.35 mIU/L), FT4 9 pmol/L (RR, 11.9 to 25.6 pmol/L) and tri-iodothyronine (FT3) 3 pmol/L (RR, 3.3 to 8.95 pmol/L).

Examination gave important clues to diagnosis. He had micropenis (thin with stretched length 2.6 cm) and small descended testes (0.5 mL), mild hypotonia, a weak cry and midfacial hypoplasia with a high arched palate.

MRI revealed absence of the anterior pituitary and an ectopic posterior pituitary, consistent with the diagnosis of multiple anterior pituitary hormone deficiency.

Treatment

Edward was commenced on levothyroxine, hydrocortisone and GH. This was followed by a rapid improvement in alertness, feeding and growth, and normalisation of liver function over two to three months.

2. Diagnostic screen for suspected hypopituitarism

- Electrolytes, urea and creatinine levels, liver function tests, blood glucose level
- Free thyroxine (FT4), free tri-iodothyronine (FT3) and thyroid stimulating hormone levels (TSH)*
- Random growth hormone (GH) level†
- Insulin-like growth factor-1 (IGF-1) level†
- Prolactin level
- Adrenocorticotrophic hormone and cortisol level (8 am sample)
- Luteinising hormone, follicle stimulating hormone and oestradiol/testosterone levels in infants under 4 months of age§

* It is essential to specify all three hormones on the lab request and note in the 'comments' box that the screen is for hypopituitarism; otherwise the lab will not measure FT4 or FT3.

† Daytime GH concentration is usually less than 3 mcg/L except in infants less than 6 months old, and in response to stress. Random GH concentrations >10 mcg/L (or 30 mU/L) in infants less than 6 months old,[4] and more than 5 mcg/L (or 15 mU/L) in older infants and children suggest GH sufficiency.

† Measurement of insulin-like growth factor binding protein 3 (IGFBP3) may have additive diagnostic value to IGF-1 because of the difficulty in interpreting IGF-1 levels in infancy, but is not rebatable on Medicare.

§ Absence of the raised levels normally observed during the physiological minipuberty in the first four months postnatally is suggestive of gonadotropin deficiency.

child with an intact thirst mechanism will seek water at the expense of either calorie-rich fluids such as milk, or food intake, causing FTT (as in Case 3). Renal sodium retention in an effort to maximise fluid retention results in an inappropriately low (often undetectable) urinary sodium for the plasma sodium; nevertheless, plasma sodium can be normal if the child is an efficient drinker.

Screening investigations for suspected DI are listed in Box 3.

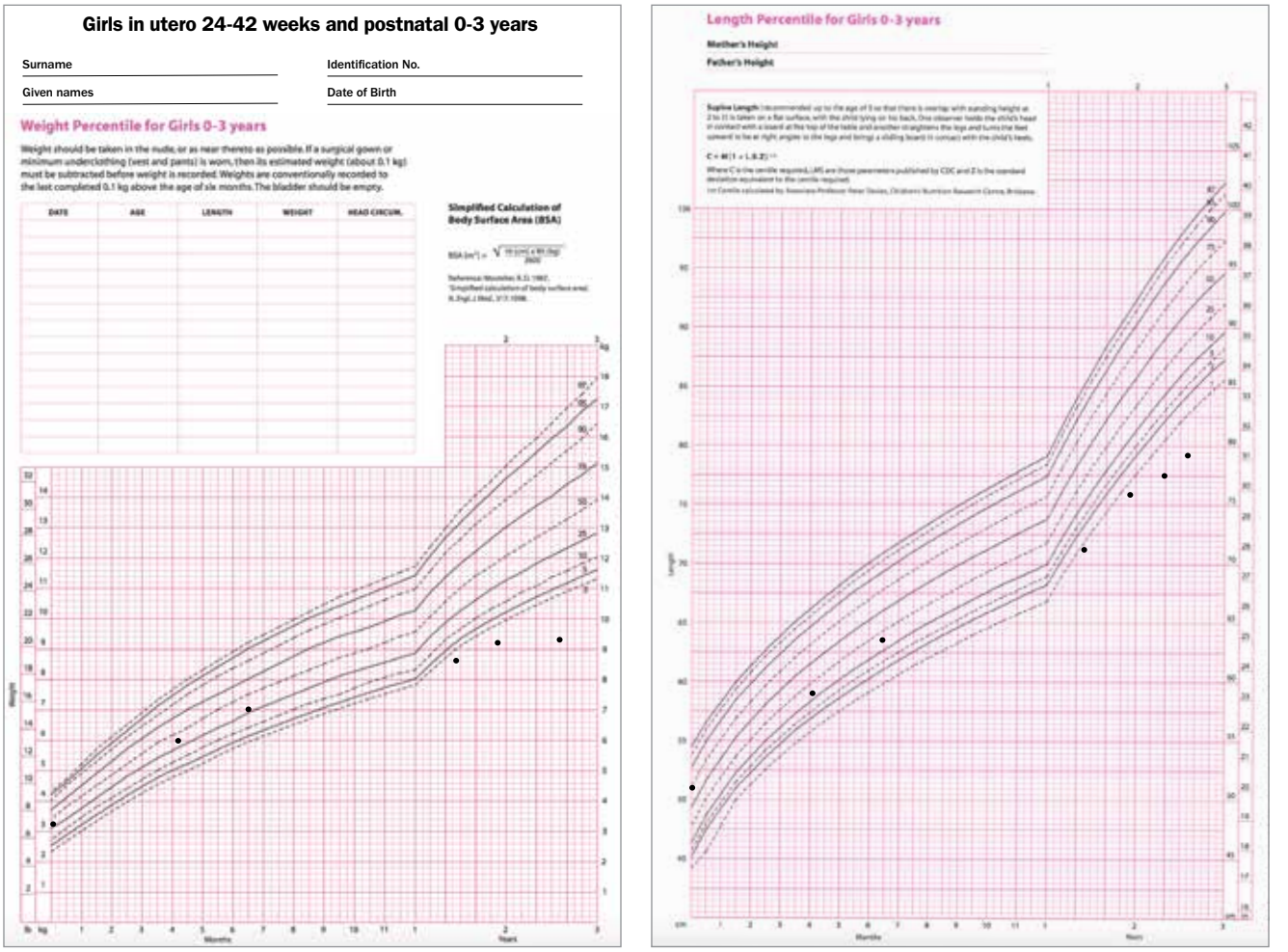
Hypercalcaemia

Hypercalcaemia has protean manifestations with anxiety and mood disturbance, non-specific aches and pains, polyuria, polydipsia and anorexia or fussy feeding causing poor weight gain. The affected infant is miserable and feeds poorly, causing FTT (see Case 4). End-organ damage due to hypercalcaemia (nephrocalcinosis, fractures or osteoporosis) by the time of diagnosis is not uncommon in children and adolescents, as the non-specific symptoms and signs such as poor weight gain, easy fatigability, depressed mood and aches and pains are easily missed.

The causes of hypercalcaemia can be divided into parathyroid hormone (PTH)-mediated and non-PTH mediated, with underlying aetiologies being different in neonates and infants compared with those in older children.

The hypercalcaemia mediated by PTH is usually severe. Neonatal severe hyperparathyroidism is, thankfully, rare, and due either to an adaptation in utero to maternal hypocalcaemia (in which case it is transient) or to homozygous inactivation of the calcium-sensing receptor (CaSR), resulting in unregulated secretion of PTH.[7] In its milder form, an inactivating mutation of the *CaSR* gene is more often associated with familial hypocalciuric hypercalcaemia (FHH; autosomal dominant); however, most individuals with this are asymptomatic.[7] Hyperparathyroidism in older children is usually sporadic (in more than 65% of cases), associated with a single parathyroid adenoma.[7] It can also be the presenting feature of the autosomal dominant multiple endocrine neoplasia (MEN) syndromes, more often type 1 than type 2, in which case there may be a family history of nephrolithiasis, renal stones or parathyroidectomy.

More often, particularly in infancy, hypercalcaemia is not mediated by PTH and a cause can be hard to pin down, hence the term, idiopathic hypercalcaemia of infancy. This may be found incidentally, or when investigating for poor feeding, irritability and FTT. Excessive vitamin D supplementation or inherited defects in vitamin D metabolism,[8,9] and excessive calcium supplementation in



Figures 2a and b. Weight and length charts of a girl diagnosed with hypopituitarism at age 2 years and 7 months.

total parenteral nutrition (TPN) or in milk fortifiers for small or premature infants, need to be excluded. Subcutaneous fat necrosis of the newborn, which may manifest as faint pink macules or the feel of subcutaneous nodules or plaques, is associated with a history of birth trauma or asphyxia. Syndromic causes such as Williams syndrome (Case 4) and various rare inborn errors of metabolism can be associated with hypercalcaemia.[10]

In older children, prolonged immobility, especially in association with fractures, causes transient hypercalcaemia.[7] Hypercalcaemia of malignancy is rare in children and mostly associated with haematological malignancies. Chronic vitamin A intoxication leads to hypercalcaemia, which also has been reported in association with vitamin A analogues used as chemotherapy for certain cancers.

Investigations to screen for hypercalcaemia are listed in Box 4.

FTT despite normal appetite

Diencephalic syndrome

Diencephalic syndrome is rare and characterised by normal linear growth and cachexia despite good appetite in a hyperalert infant. It is most often associated with large hypothalamic or optic pathway gliomas, but not necessarily detectable hormonal abnormality (Case 5).[11,12] Decreased subcutaneous fat contributes to the emaciated appearance of infants with diencephalic syndrome, but investigations do not show any micronutrient deficiencies otherwise associated with decreased nutritional intake.

The cause of the FTT despite a good appetite has not been elucidated. Theories on its pathogenesis include increased GH levels, partial GH resistance, increased lipolysis and increased energy expenditure.

Diagnostic screening for diencephalic syndrome includes the investigations listed for hypopituitarism in Box 2, as well as a cerebral MRI.

Psychosocial dwarfism

The spectrum of psychosocial dwarfism is rather more common than diencephalic syndrome but usually associated with linear growth failure rather than poor weight gain, so strictly speaking is not a form of FTT. Appetite can be voracious but affected infants often have abnormal eating behaviour and vomiting in addition to other behavioural disturbance. Impaired emotional-cognitive development is common. In its extreme form, there are

Case 3. Diabetes insipidus

Presentation

Claude was referred by his gastroenterologist for endocrine review at 15 months of age. In early infancy, first his weight gain and subsequently his linear growth moved from the 25th and 10th percentiles, respectively, at 2 months to well below the 3rd percentile for both by 15 months of age. He was changed from breast feeds to formula at age 2 months because of crying and irritability, after which he vomited frequently and became extremely constipated. Starting solids was accompanied by choking and gagging. Because of her own preference for water, his mother gave him frequent bottles of water and once he was able to communicate his needs, he would demand water before eating anything.

The family history was significant. His mother drank up to 6L of water a day during pregnancy and had polyhydramnios. Her brother had a history of unquenchable thirst for water and was intellectually disabled. Her grandfather was also an enthusiastic water drinker and died relatively young of a stroke.

Investigations

At 17 months, Claude was morphologically and developmentally normal. After a four-hour fast, his plasma sodium was 150 mmol/L (reference range [RR], 137 to 147 mmol/L) with an osmolality of 310 mmol/kg (RR, 280 to 300 mmol/kg) and the accompanying urine had a sodium concentration of 7 mmol/L and an osmolality of 90 mmol/kg, consistent with diabetes insipidus.

Further investigations revealed that his diabetes insipidus was nephrogenic rather than central, in keeping with the X-linked pattern of inheritance. Subsequently, this was confirmed on genetic testing (a mutation in the *AVPR2* gene).

Treatment

Claude was treated initially with hydrochlorothiazide and subsequently with indomethacin.

identifiable pituitary hormone abnormalities including central (pituitary) hypothyroidism, low insulin-like growth factor-1 (IGF-1) and GH deficiency on dynamic testing.

Psychosocial dwarfism is thought to be mediated by the hypothalamic effects of chronic stress.[13,14] Growth does not respond to GH treatment but all pituitary abnormalities resolve with resolution of the adverse social circumstances.[13]

The diagnosis of psychosocial dwarfism is based on suggestive history and, importantly, on establishing reversal of growth failure after removal of the psychosocial stressor. Hypopituitarism must be excluded with screening as suggested in Box 2.

Case 4. Hypercalcaemia

Presentation

Beatrice was a full-term, well-grown baby at birth but fed poorly, vomited and was extremely irritable. She was initially breast fed but then had repeated changes in formula because of continued vomiting and irritability. She would gag and refuse to eat when solids were introduced. From the age of 3 to 4 months she was extremely constipated.

Over the first year, her linear growth proceeded along the 25th percentile. Her weight also followed the 25th percentile until the age of 7 months, but had dropped below the 3rd percentile by 12 months. She was delayed in her motor milestones, unable to sit unsupported at 12 months.

Investigations

Initial investigations were unrevealing, leading to a gastroenterology referral for endoscopy. This was normal but a biochemical panel taken at the time of anaesthesia showed hypercalcaemia (serum calcium concentration 3.84 mmol/L; reference range, 2.2 to 2.7 mmol/L). Beatrice had subtle facial dysmorphism consistent with Williams syndrome, which was confirmed on genetic testing.

Treatment

Beatrice responded well to a low calcium formula but needed restriction of dairy foods for many years.

3. Diagnostic screen for suspected diabetes insipidus

- Morning paired electrolytes, urea and creatinine/serum osmolality levels and urine electrolytes/osmolality levels (after a 6 to 8 hour overnight fast)*
- Fluid balance assessment (parent diary)
- Consider early endocrine referral for infants or toddlers/children who show a preference for large amounts of water, drink water from inappropriate places or wake up to drink water overnight

* For infants and older children who drink a large amount of water overnight, this may need to be conducted in hospital.

FTT associated with increased metabolic need

Diabetes mellitus

The main endocrine aetiology in FTT associated with increased metabolic need is type 1 diabetes mellitus, most often due to autoimmune destruction of the insulin-producing islet cells. Diabetes can develop at any age, including in neonates and infants, in whom a monogenic cause is more likely; however, until a specific genetic cause is established, insulin remains the appropriate treatment.

4. Diagnostic screen for suspected hypercalcaemia

- Electrolytes, urea and creatinine; calcium, magnesium and phosphate; albumin; alkaline phosphatase; parathyroid hormone and 25-hydroxyvitamin D levels
- Urinary calcium to creatinine ratio
- Screen parents if hypercalcaemia present
- Consider fluorescence in-situ hybridisation (FISH) for Williams syndrome

Without the anabolic action of insulin, glucose is lost in the urine and the net catabolic effect leads to weight loss in a child who is eating and drinking voraciously. The absence of insulin allows uncontrolled ketogenesis, leading to life-threatening acidosis and metabolic derangement, so this is an important diagnosis to not delay or miss. As shown in Case 6, the diagnosis may be delayed with life-threatening consequences when there are other plausible causes of weight loss such as psychiatric comorbidity or developmental delay.

The key to making the diagnosis is to consider it. The next step is a urine dipstick for glucosuria (and ketonuria) or a capillary (finger-prick) blood glucose test and, if possible, measurement of ketones. These should be performed in the office.

Investigations to screen for diabetes mellitus are listed in Box 5.

Hyperthyroidism

Hyperthyroidism at any age is associated with weight loss or poor weight gain despite a big appetite, because of the increased metabolic rate. The most common symptoms described beyond infancy are anxiety, restlessness, poor sleep, weakness and decreased exercise tolerance. Signs elicited on examination include tachycardia, warm sweaty hands, fine tremor, rapid correcting reflexes, exophthalmos, lid-lag and conjunctival chemosis. The neonate presents with poor weight gain, irritability, jitteriness and tachycardia. The most common aetiology is autoimmune thyroid disease, with hyperthyroidism caused by antibodies (thyrotropin-receptor antibodies; TRAb) stimulating the thyroid stimulating hormone (TSH) receptor.

Neonatal hyperthyroidism is usually due to transplacental passage of TRAb from mother to fetus. There should be a history of maternal hyperthyroid autoimmune thyroid disease (Graves' disease). The onset of neonatal hyperthyroidism may be delayed when the mother is taking significant doses of antithyroid medications as these also cross the placenta and affect the newborn's thyroid; hence infant review about the age of day 5 with repeat thyroid function testing is crucial.

Rarely, hyperthyroidism is due to an activating mutation of the TSH receptor. Inheritance is autosomal dominant (but it can be sporadic), so there may be a family history, but, importantly, the timing of onset is variable, even within kindreds.

Although modern TRAb assays have very high sensitivity and specificity, they are not perfect,[16] and infant follow up should be guided

Case 5. Diencephalic syndrome

Presentation

Georgina was investigated for poor weight gain with continued linear growth and tall stature in the second six months of life. A gluten-free diet after coeliac disease was diagnosed endoscopically did not improve her weight gain, leading to an admission at 15 months for further investigation. On examination, Georgina was a developmentally normal, happy, interactive and hyperalert infant with a length above the 97th percentile and weight below the 3rd percentile. Nystagmus was noted.

Investigations

MRI revealed a large hypothalamic tumour. Bloods showed normal anterior and posterior pituitary function, a presentation consistent with diencephalic syndrome.

Treatment

Treatment over many years involved surgery and chemotherapy.

Case 6. Diabetes mellitus

Presentation

Henry, aged 13 years, presented to the emergency department when his pre-existing weakness and abdominal pain became worse during a sports game. During the previous two months he had barely attended school due to malaise and frequent abdominal pain. He was diagnosed with an anxiety disorder triggered by his recent change to high school, and was started on sertraline.

In the emergency department he looked anxious, emaciated and unwell. His weight was 39 kg (3rd to 10th percentile) and height 160 cm (25th percentile). The triage nurse noted his tachypnoea (32 breaths/minute) without increased work of breathing, and tachycardia (110 beats/minute).

Investigations

Urine dipstick showed glucose and ketones in the urine, which led to a finger-prick test that showed a high ketone level of 6.7 mmol/L and glucose that was 'HI'. Further bloods showed a glucose concentration of 48 mmol/L, severe metabolic acidosis and deranged electrolytes.

Treatment

Treatment with fluid resuscitation and insulin was started, according to the hospital protocol for diabetic ketoacidosis. Autoantibodies associated with type 1 diabetes obtained before the initiation of insulin treatment confirmed the diagnosis of type 1 diabetes.

5. Diagnostic screen for diabetes mellitus

- Bedside measurements: capillary or urinary glucose and ketone levels. A random blood glucose level (BGL) 11.1 mmol/L or above is diagnostic of diabetes and above 7.1 mmol/L suspicious; however, a child with a random BGL above 10 mmol/L, particularly in the presence of ketones greater than 1.5 mmol/L, should be referred to an emergency department for further assessment.[15] There is no role for referral to a pathology laboratory or an outpatient clinic if type 1 diabetes is suspected.
- Symptoms and signs include:
  - increased thirst, bed-wetting
  - weight loss or failure to gain weight despite normal or increased intake
  - fatigue/lethargy
  - abdominal pain
  - blurred vision (due to hyperglycaemia)
  - increased rate and depth of breathing (Kussmaul breathing)

Case 7. Hyperthyroidism

Presentation

Albert was born at term with birth weight and length on the 50th percentile after a pregnancy complicated by maternal hyperthyroidism thought to be thyroid receptor antibody (TRAb) negative. The mother was being treated with propylthiouracil. Albert's thyroid function tests (TFTs) at 3 days of age were normal for age (thyroid stimulating hormone [TSH] 3.34 mU/L, free thyroxine [FT4] 28.7 pmol/L) and he was discharged for routine follow up at 6 weeks of age.

In the interim he was irritable and difficult to settle, he fed up to eight times per day with breast feeds followed by supplementation with formula and he vomited after feeds. His weight gain was very poor, although his linear growth proceeded along the 50th percentile and at 3 weeks of age he was below birth weight. He presented to the emergency department at his local hospital.

Investigations

Investigations for pyloric stenosis were negative. At 6 weeks, TFTs showed Albert to be hyperthyroid (TSH undetectable, tri-iodothyronine [FT3] 16 pmol/L, and FT4 35 pmol/L). Subsequent testing in a different assay showed both mother and baby to be TRAb positive.

Treatment

Albert responded to treatment with Lugol's iodine and carbimazole and the hyperthyroidism resolved as expected after several months when the maternal antibodies disappeared.

by the clinical history, not just serological findings to avoid late diagnosis, as shown in Case 7. Missed neonatal thyrotoxicosis can have irreversible consequences including heart failure and craniosynostosis.

TRAb-positive neonatal thyrotoxicosis resolves once maternal antibodies disappear from the infant's circulation within a few months.

6. Diagnostic screen for hyperthyroidism

Neonatal

- Cord thyroid receptor antibody (TRAb) if mother is known to be TRAb positive or her status is unknown
- Day 3 to 5: thyroxine (FT4), tri-iodothyronine (FT3), thyroid stimulating hormone (TSH)* and TRAb if not checked on cord blood

Older children

- FT4, FT3, TSH*
- TRAb
- Antimicrosomal/thyroid peroxidase antibodies
- Antithyroglobulin antibodies

* To avoid the possibility of a child being recalled for blood collection, it is advisable to specify all three hormones on the lab request and note in the 'comments' box that the screen is for autoimmune hyperthyroidism (Graves' disease).

The diagnostic screening investigations for suspected hyperthyroidism are listed in Box 6.

Summary

In children of any age with FTT, general screening investigations including serum electrolytes, calcium, phosphate and glucose levels; liver function tests; and full thyroid function tests, together with a good history and examination, will provide a reasonable indication of whether an endocrine abnormality is likely.

There are many caveats to the interpretation of endocrine investigations and if an endocrine cause is thought likely, early consultation with an endocrinologist is advisable. On the other hand, because most children will have another explanation for their poor weight gain, consultation with a general paediatrician may be of most help in the first instance. **ET**

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