Case 1: Severe acne – not just skin deep

A previously healthy 10-year-old girl presented to a paediatric dermatologist with a three-year history of facial acne resistant to medical therapy. At seven years of age, she developed acne on her face, back and thorax that progressively worsened despite adherence to topical face creams and a trial of minocycline (Minocin, Triax Pharmaceuticals, USA). On further history, she developed pubic hair at seven years of age and axillary hair soon after. Early breast development was noted at nine years of age, but she was premenarcheal at the time of consultation. She denied a significant growth spurt, but her parents noted that at 10 years of age, she was the tallest girl in her peer group and the same height as her 15-year-old sister. Her mother's height was 170.2 cm and her father's height was 172.7 cm, giving her a midparental height of 165.1 cm (just above the 50th percentile). Her mother and sister both reached menarche at 12 years of age.

On examination, she had acne with open and closed comedones on her face, chest and back. Her height was 145 cm (just above the 75th percentile) and weight was 45.8 kg (at the 90th percentile). Her thyroid was not enlarged. She had Tanner stage 3 breast development, Tanner stage 4 pubic hair growth and a heavy growth of axillary hair. She had normal female genitalia with no clitoromegaly. Further investigations were performed.

Case 2: A pale infant – not a typical case of iron deficiency

A 15-month-old boy presented to his doctor when his mother became concerned about his diet. Despite the introduction of solids at six months of age, he was almost exclusively breastfed and a 'picky eater'. His parents were partial vegetarians, with little meat intake. His mother had noticed that he was pale with gait disturbance and occasional falls. His developmental history was otherwise unremarkable. His past medical history included a term delivery with no complications and an uneventful postnatal period. After initial bloodwork, he was referred to a paediatric hematologist.

On examination, he was pale. His weight and height were between the 5th to 10th and 15th percentiles, respectively. A systolic murmur grade 2/6 was present. The patient's bloodwork included a complete blood count with white blood cell count 5.2×10^9/L (normal 5.3×10^9/L to 16×10^9/L), neutrophils 1×10^9/L (normal 1×10^9/L to 6.5×10^9/L), hemoglobin 83 g/L (normal 103 g/L to 135 g/L), mean corpuscular volume 107 fL (normal 70 fL to 86 fL) and platelet count 311×10^9/L (normal 200×10^9/L to 550×10^9/L). His reticulocyte count was 31×10^9/L (normal 40×10^9/L to 120×10^9/L), and his peripheral blood smear showed occasional oval macrocytes and hypersegmented neutrophils. A bone marrow aspirate was performed, and the images demonstrated classic findings of a particular diagnosis.

Correspondence: Dr Jeremy Friedman, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario M5G 1X8.
Telephone 416-813-7368, fax 416-813-5663, e-mail jeremy.friedman@sickkids.ca
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CASE DIAGNOSIS: LATE-ONSET CONGENITAL ADRENAL HYPERPLASIA

X-rays revealed that at a chronological age of 10 years and one month, the patient's bone age was equivalent to that of a 12-year-old child. Her abdominal and pelvic ultrasound were normal, with no evidence of polycystic ovaries. Her thyroid function tests were normal, and estradiol level was normal at 69 pmol/L. The patient's adrenocorticotropic hormone (ACTH) stimulation test revealed an adequate cortisol response, with an increase from 467 nmol/L to 581 nmol/L at 60 min stimulation. Random luteinizing hormone level was low at 2.0 U/L (normal 3 U/L to 17 U/L) and follicle-stimulating hormone level was 4.8 U/L (normal 0 U/L to 9 U/L). Her testosterone level was also normal at 1.6 nmol/L (lower than 2.1 nmol/L), but her dehydroepiandrosterone (DHEAS) level was elevated at 9.0 µmol/L (normal 0 µmol/L to 7.9 µmol/L). The patient's baseline 17-hydroxyprogesterone (17-OHP) level was 90.7 nmol/L (normal 0 µmol/L to 5.9 nmol/L) and stimulated to 125.9 nmol/L following a 60 min ACTH stimulation test. With these findings, a diagnosis of late-onset congenital adrenal hyperplasia (CAH) was established.

Late-onset CAH, also known as nonclassic CAH, is an autosomal recessive disorder characterized by virilization, premature adrenarche, advanced bone age and reduced fertility. Late-onset CAH is an allelic variant of classic CAH; however, the presentation is markedly different. Females with classic CAH present with ambiguous genitalia at birth. Males with the classic variant may appear phenotypically normal at birth, but typically present by four weeks of age with failure to thrive, dehydration, hyponatremia and hyperkalemia if they have the 'salt-wasting' form. Despite the significant difference in phenotypic presentation, both classic CAH and late-onset CAH result from 21-hydroxylase deficiency. The resultant deficiency of hormones downstream from 21-hydroxylase decreases the negative feedback on the hypothalamic-pituitary axis. Consequently, ACTH secretion increases, leading to excess stimulation of the adrenal glands to secrete adrenal androgens. The excess androgens result in virilization.

It is generally more challenging to establish a diagnosis of late-onset CAH than of classic CAH. In classic CAH, baseline 17-OHP levels are elevated; however, in late-onset CAH, the baseline 17-OHP levels may be normal. In these patients, an elevated 60 min 17-OHP level on an ACTH stimulation test is required for diagnosis.

The age of onset is quite variable, with signs and symptoms presenting any time from childhood to adulthood. The presentation of late-onset CAH also differs between women and men. Among women, late-onset CAH may present with hirsutism, early growth spurt, menstrual irregularities, male-patterned baldness, short stature secondary to early epiphyseal closure or severe acne. The phenotypic presentation is similar to polycystic ovarian syndrome (PCOS) and, therefore, the two diagnoses are often indistinguishable clinically. Whereas PCOS is estimated to affect 6.5% to 8% of women, late-onset CAH reportedly affects 0.1% to 1% of women, with higher prevalence among certain ethnic groups including members of the Ashkenazi Jewish, Mediterranean and Hispanic populations. However, with increasing recognition of late-onset CAH as a clinical entity and more widespread administration of ACTH stimulation testing among patients with phenotypic hyperandrogenism, current evidence suggests that PCOS and late-onset CAH may be over- and underdiagnosed, respectively.

Among men, acne may be the only phenotypic feature of hyperandrogenism, posing an even greater challenge to the clinician to establish a diagnosis. These patients typically present with acne resistant to topical and systemic treatment. Detailed history may reveal early puberty, and the bone age may be advanced. Similar to females, males with late-onset CAH have an elevated 17-OHP level on ACTH stimulation testing. Because males typically present with acne in isolation, an even higher index of suspicion may be necessary to establish the underlying diagnosis.

Once a diagnosis of late-onset CAH is established, the primary goals of management of the female patient are to minimize androgen production, achieve maximum growth potential and prevent virilization. Late-onset CAH is primarily treated with oral glucocorticoids, which are particularly efficacious in the treatment of associated acne and anovulatory infertility. If, however, the primary concern is hirsutism, antiandrogen therapy is recommended. Among male late-onset CAH patients, glucocorticoid therapy is indicated in the presence of testicular adrenal rest tumours, oligospermia and resistant acne.

On initiation of therapy, close monitoring of clinical parameters including growth, virilization, blood pressure and bone age are essential. Biochemical markers, including 17-OHP, cortisol, ACTH, androstenedione, testosterone, and DHEAS levels, can also be useful to monitor response to treatment. The administration of stress-dose glucocorticoids to late-onset CAH patients during intercurrent illness perioperatively and during other periods of stress is controversial, but is practiced at some centres.

Finally, it is imperative that clinicians consider rare but concerning causes of hyperandrogenism, early puberty or virilization. Rapidly progressive symptoms of hyperandrogenism should prompt the clinician to investigate for androgen-secreting tumours as an underlying etiology. High total testosterone or DHEAS levels in the presence of normal 17-OHP levels should similarly prompt referral to a specialist for further assessment.

CLINICAL PEARLS

- Consider underlying endocrine disorders in the presence of acne that persists despite medical management. In females, consider PCOS or late-onset CAH, and in males consider late-onset CAH.
- When a child presents with any symptom of early adrenarche, ensure a detailed pubertal history is ascertained and consider testing for baseline and, if necessary, ACTH-stimulated 17-OHP levels.

- PCOS and late-onset CAH are virtually indistinguishable clinically; therefore, female patients with late-onset CAH are often mistakenly diagnosed with PCOS. Baseline and ACTH-stimulated 17-OHP levels are necessary to confirm or exclude the diagnosis of late-onset CAH.

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Deena Savlov BSc MD,
Department of Paediatrics,
University of Toronto, Hospital for Sick Children,
Toronto, Ontario

Clodagh O'Gorman MB BCH BAO MRCPI MSc,
Stacey Urbach MD MPH FRCPC,
Division of Endocrinology,
University of Toronto, Hospital for Sick Children,
Toronto, Ontario

Elena Pope MSc FRCPC,
Section of Dermatology, Division of Paediatric Medicine,
University of Toronto, Hospital for Sick Children,
Toronto, Ontario

CASE 2 DIAGNOSIS: MEGALOBLASTIC ANEMIA DUE TO DIETARY COBALAMIN DEFICIENCY

Additional investigations for macrocytic anemia included serum folate 33.3 nmol/L (normal greater than 6.8 nmol/L), and vitamin B_{12} (cobalamin) 44 pmol/L (deficient range lower than 107 pmol/L). Based on the test results and the bone marrow aspirate findings of hypersegmented neutrophils, megaloblasts and giant metamyelocytes, a diagnosis of megaloblastic anemia (MA) was made.

Bloodwork was also performed on the mother. Serum folate was normal at 30.9 nmol/L (greater than 6.81 nmol/L) and serum vitamin B_{12} was low-normal at 209 pmol/L (normal 133 pmol/L to 675 pmol/L). Maternal hemoglobin level and mean corpuscular volume (MCV) were normal.

Given the history, the likely cause of MA and cobalamin deficiency was reduced dietary intake. The toddler was treated with intramuscular cyanocobalamin injections (20 µg daily for seven days, then 100 µg weekly for four weeks) and a dietician was consulted. Oral cobalamin therapy was also an option and would have been effective, but for convenience and to ensure compliance, the parenteral route was chosen.

Two months later, he had improved significantly with a normal hemoglobin level (107 g/L) and MCV (83 fl). He was more energetic and interactive. His gait had returned to normal and his falls had decreased. His diet had improved with increased intake of meats, eggs, milk, fruits and vegetables, supplemented with PediaSure (Abbott Nutrition, Canada). Eight months after presentation, his development was appropriate for age and he was not anemic, despite being off therapy for several months. Maintenance of normal counts after discontinuation of therapy and adherence to a balanced diet are consistent with a dietary etiology for MA.

MA describes a group of disorders characterized by defective DNA synthesis. Morphological hallmarks in the marrow are megaloblasts and giant metamyelocytes displaying nuclear to cytoplasmic asynchrony. A megaloblast has a nucleus that is immature relative to the cytoplasm because the nucleus has impaired DNA synthesis, but hemoglobinization, which is dependant on ribosomal function, continues normally in the cytoplasm. There are many causes of MA, some of which are listed in Table 1.

The case described demonstrates MA in a paediatric patient who was a 'picky eater' and was found to have macrocytic anemia. The insidious onset can delay diagnosis. It is important to diagnose this condition early to avoid the symptoms of anemia, as well as the neurological sequelae, including loss of vibration sensation and potential progression to spastic ataxia due to demyelination of the dorsal and lateral columns of the spinal cord. An approach to the workup of suspected MA in paediatric patients is proposed.

History and physical examination

Many patients are asymptomatic, and a diagnosis of MA is made incidentally when macrocytosis is found on routine bloodwork. There may be a history of poor food intake, prolonged breastfeeding, and a maternal history of vegetarian and vegan diets or autoimmune disorders. Nonspecific symptoms include irritability, weight loss, diarrhea or constipation. The clinical features are primarily those of a classic 'lemon yellow' pallor because of the combination of anemia and jaundice. Severe cases may have marked anorexia, weight loss, glossitis and angular cheilosis. Neurological effects may be manifested by failure to reach developmental milestones and may include paresthesias, muscle weakness and impaired intellectual development.

Screening bloodwork

The complete blood count shows macrocytic anemia. The MCV can be normal when there is concomitant microcytosis (thalassemia trait or iron deficiency). The peripheral blood smear shows oval macrocytes and hypersegmented neutrophils (five or more lobes) (Figure 1). If a child is being breastfed, maternal bloodwork must be performed to exclude maternal vitamin deficiencies.

Diagnostic tests

Folate and cobalamin levels are critical diagnostic blood tests. Red blood cell folate levels may be a better indicator of body folate because recent changes in dietary intake and hemolysis of the specimen will interfere with serum folate levels. Patients deficient in folate have low assay results, but a significant proportion of cobalamin-deficient patients will also have low red cell folate assays because cobalamin is a cofactor in folate metabolism. Cobalamin assays have limitations when correlating clinical deficiency with low-normal assay levels in some patients. Concentrations of the

TABLE 1
Causes of megaloblastic anemia

Etiology	Cobalamin deficiency	Folate deficiency
Nutrition	Strict vegetarianism or vegan diets	Malnutrition in elderly, alcoholics, impoverished communities
Gastrointestinal abnormalities	Gastric atrophy: achlorhydria	Celiac disease
	Intrinsic factor deficiency – congenital or acquired abnormality	Dermatitis herpetiformis
	Total or partial gastrectomy	Tropical sprue
	Bacterial overgrowth in the small bowel (achlorhydria, anatomical defects, impaired motility)	Extensive jejunal resection
	Terminal ileal resection	Crohn's disease
	Crohn's disease	
	Extensive celiac disease	
	Zollinger-Ellison syndrome	
	Pancreatic insufficiency	
	Fish tapeworm (*Diphyllobothrium latum*)	
	HIV	
	Congenital defects (eg, Imerslund-Gräsbeck syndrome)	
Drugs	Proton pump inhibitors	Cytotoxics (eg, methotrexate)
	Metformin	Antibiotics (eg, nitrofurantoin, tetracycline)
	Phenformin	Anticonvulsants (eg, phenytoin, carbamazepine)
	Anticonvulsants	
	Cytotoxic drugs	
Increased utilization/loss	Pregnancy	Pregnancy
		Chronic hemolysis
		Exfoliative dermatitis
Metabolic abnormalities	Congenital transcobalamin II deficiency or functional abnormality	Congenital folate malabsorption
	Congenital intrinsic factor deficiency	Dihydrofolate reductase deficiency

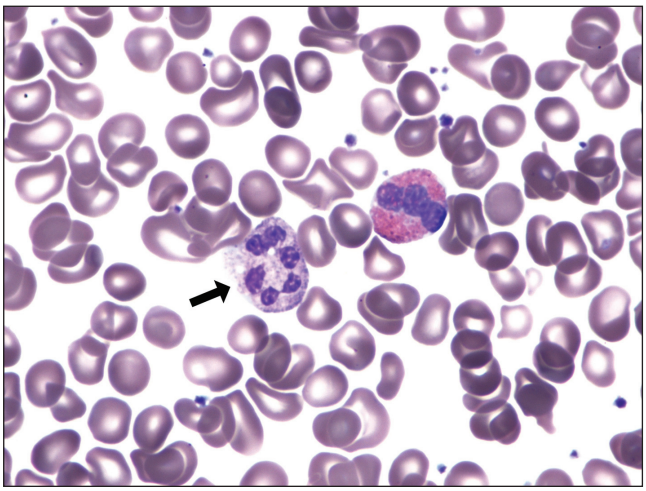

Figure 1) *Peripheral blood smear demonstrating a hypersegmented neutrophil*

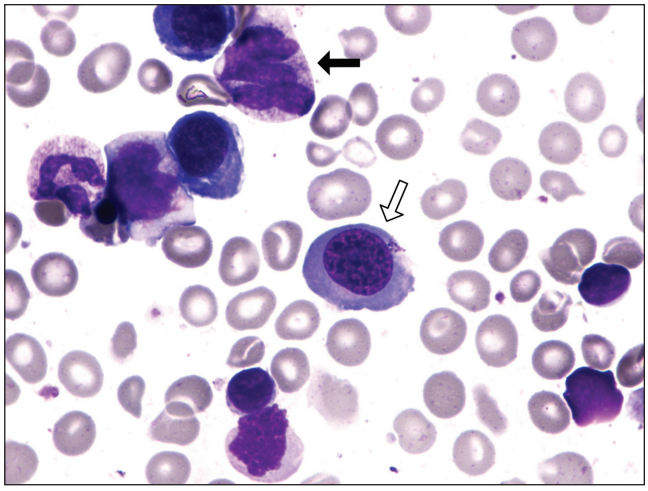

Figure 2) *Bone marrow aspirate demonstrating megaloblastic hematopoiesis with a megaloblast (white arrow) and a giant metamyelocyte (black arrow)*

cobalamin carrier protein transcobalamin 1 can influence serum levels of vitamin B_{12}. The assays for folate and vitamin B_{12} levels are generally robust and convenient for diagnosing deficient states.

A bone marrow biopsy is an invasive procedure and less frequently performed with the availability of diagnostic blood tests, but it can be warranted to expedite diagnosis. The marrow can provide a morphological diagnosis within a matter of minutes; however, it requires skilled physician resources. A bone marrow aspirate in MA shows hypercellularity with ineffective hematopoiesis and megaloblastic erythropoiesis (Figure 2), giant myeloid precursors (giant metamyelocytes) (Figures 2 and 3), increased iron stores and, less commonly, hyperpolyploid megakaryocytes. When no explanation for cytopenias is found, bone marrow studies must be performed to exclude bone marrow failure, hematological malignancy or metastatic tumour.

Additional tests and special tests

Schilling test: When Addisonian pernicious anemia (PA) is suspected, a Schilling test may be performed to assess

cobalamin absorption. The test measures urinary excretion of orally administered radioactive cobalamin, with and without added intrinsic factor. PA is rare in children. The Schilling test would be helpful, and should be performed when there is a need to distinguish PA from the rarer malabsorptive errors of cobalamin absorption that are listed in Table 1.

Total plasma homocysteine, serum methylmalonate and urinary excretion of methylmalonate: Vitamin B_{12}, but not folate, is required in methylmalonate (MMA) metabolism. Increased total plasma homocysteine and MMA levels are associated with cobalamin deficiency. Total plasma homocysteine level is elevated in both folate and vitamin B_{12} deficiency, and is less specific than MMA. These tests, however, may be useful in suspected presymptomatic deficiency when the patient is not anemic and cobalamin levels are in the low-normal range. Elevated total plasma homocysteine and MMA levels may signal functional vitamin B_{12} deficiency (1). Availability of these tests may limit their diagnostic application.

The etiology of folate or cobalamin deficiency must be determined because most causes are preventable or treatable. In developed countries, MA is more commonly caused by cobalamin rather than folate deficiency because many foods are folate-supplemented. Cobalamin deficiency must be ruled out before administering folic acid because treatment with folic acid alone, in the presence of cobalamin deficiency, can cause or exacerbate irreversible neurological damage.

MA can occur in children when there is a history of 'picky eating', poverty, chronic hemolysis such as hereditary spherocytosis, diets low in animal products or prolonged breastfeeding. Human milk cobalamin concentrations have been found to be lower in vegetarian mothers compared with omnivorous mothers (2). Breastfeeding mothers can have clinical (3) or subclinical cobalamin deficiency, the latter having low-normal cobalamin levels (1). As such, infants of cobalamin-deficient mothers are at risk of developing MA. Cobalamin deficiency may also occur in infants born to mothers with PA; however, this risk is largely theoretical because women with PA are usually infertile (4).

Early diagnosis of MA in childhood is imperative to prevent neurological consequences in infants who remain untreated. Increased awareness leading to early diagnosis and appropriate, timely therapy can prevent irreversible neurological effects for the child with MA. This is especially important during the critical period of neurodevelopment in early childhood.

CLINICAL PEARLS

- Prolonged breastfed infants may be at risk of developing MA, especially if the mother consumes a vegetarian or vegan diet.

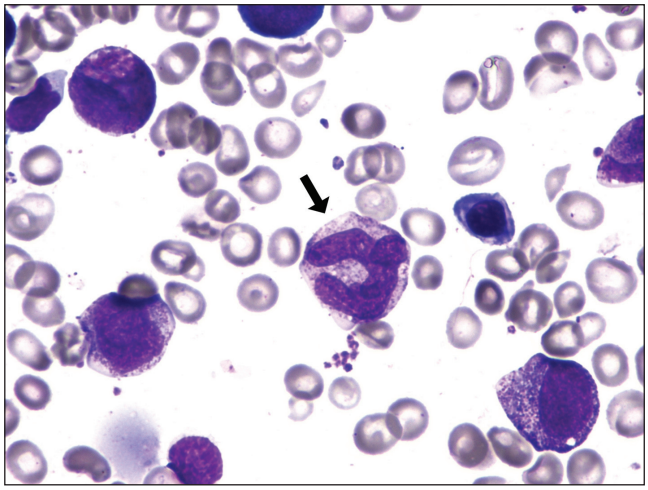

Figure 3) *Bone marrow aspirate demonstrating megaloblastic hematopoiesis with a giant metamyelocyte (black arrow)*

- Cobalamin deficiency must be ruled out before instituting folate therapy.
- Cobalamin deficiency may have neuropsychiatric as well as hematological manifestations, and early diagnosis is imperative to prevent irreversible neurological damage.
- Measurement of serum MMA is important in the detection of presymptomatic cobalamin deficiency.

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Michelle P Wong MD FRCPC,
Louis Wadsworth MB ChB FRCPath FRCPC,
Department of Pathology & Laboratory Medicine, Hematopathology,
BC Children's Hospital, University of British Columbia,
Vancouver, British Columbia

John K Wu MBBS MSc FRCPC,
David Dix MBChB FRCPC FAAP,
Department of Pediatrics,
Division of Hematology/Oncology/Bone Marrow Transplant,
BC Children's Hospital, University of British Columbia,
Vancouver, British Columbia