Gonadotrophin abnormalities in an infant with Lowe syndrome

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Summary

This case, presenting with bilateral impalpable testes, illustrates the relevance of a broad differential disorders of sex development case management. It provides new insights on hypothalamic–pituitary–gonadal (HPG) axis and testicular function abnormalities in the multisystem disorder of Lowe syndrome. Lowe syndrome, also known as oculocerebrorenal syndrome, is a rare disorder characterised by eye abnormalities, central nervous system involvement and proximal renal tubular acidosis. There are a handful of reports of pubertal delay, infertility and cryptorchidism in Lowe syndrome. Biochemistry aged 72 h: testosterone 6.4 nmol/L, LH <0.5 IU/L and FSH <0.5 IU/L. Gonadotropin-releasing hormone stimulation test identified significantly raised baseline LH = 45.4 IU/L (contrasts with earlier undetectable LH), with a 20% increase on stimulation, while baseline FSH = 4.3 IU/L with no increase on stimulation. Day 14 HCG stimulation test produced an acceptable 50% increase in testosterone. The constellation of further abnormalities suggested Lowe syndrome: hypotonia, bilateral cataracts (surgical extraction and intraocular lens implantation) and renal tubular acidosis (microscopic haematuria, hypercalciuria, proteinuria, generalised aminoaciduria, hypophosphataemia and metabolic acidosis). DNA sequencing identified de novo hemizygous frameshift mutation OCRL c.2409_2410delCT in exon 22.

Interpretation of initial and repeat GnRH and HCG testing indicates the likelihood of testicular failure. Partial testicular descent occurred but left orchidopexy was required. Improving long-term gonadal function in Lowe syndrome assumes increased importance for current cohorts as advances in renal replacement therapy have greatly improved life expectancy. Noting HPG axis abnormalities in Lowe syndrome in infancy can identify cases requiring increased surveillance of pubertal progress for earlier detection and management.

Learning points:

• Clinical endocrine problems in Lowe syndrome has been reported, but has focused on abnormalities in adolescence and young adulthood: pubertal delay and infertility.
• We present an infant with isolated LH elevation at baseline and on GnRH stimulation testing who also had bilateral impalpable testes.
• Early testing of the HPG axis in patients with Lowe syndrome may help predict gonadal abnormalities from a younger age, which will enhance the overall case management into adolescence.

Background

This case brings new information on endocrine abnormalities of the hypothalamic–pituitary–gonadal (HPG) axis and concern regarding testicular function, items not prominent or detailed in the existing literature on Lowe syndrome. Lowe syndrome, also known as oculocerebrorenal syndrome, is a rare disorder with an estimated prevalence of 1 in 500,000 (1). Patients experience multisystem morbidity from birth, and life expectancy is reduced to...
mid-adulthood. The affected gene in Lowe syndrome is OCRL1 that codes for the phosphatidylinositol (4, 5) bisphosphate 5 phosphatase enzyme. Mutations include in-frame deletions, missense mutations, premature stop codons, frameshift mutations and genomic or exon deletions (2). Inheritance is X-linked and males are almost uniquely affected. Approximately a third of cases arise from de novo mutations, but mosaicism from germline or somatic mutation has been reported in about 5% of patients (3). The syndrome is characterised by eye abnormalities, central nervous system involvement and proximal renal tubular acidosis. Hypotonia and bilateral cataracts are usually identified at birth; proximal renal tubulopathy presents over subsequent weeks or months. Other features include characteristic facial dysmorphism of frontal bossing, deep set eyes and elongated face, as well as mental retardation and seizures (1, 4). Prognosis is poor, with considerable morbidity and reduced life expectancy as a consequence of renal disease, hypotonia and susceptibility to infections. Mortality peaks in infancy and then between the second and fourth decades (1).

The endocrine stimulation tests in this infant with bilateral impalpable testes produced some unexpected results; analysis and discussion of the results provide insight to Lowe syndrome and also into some of the caveats of tests performed in disorders of sex development (DSD) management.

**Case presentation**

This term infant was born by spontaneous vaginal delivery after an uncomplicated pregnancy, with a normal birth weight of 2.61 kg. He was noted to have bilateral impalpable testes with underdeveloped scrotum but normal-size phallus. Additional signs were mild dysmorphic features (flat nasal bridge, widely spaced nipples and a deep chin cleft), hypotonia, bilateral absent red reflex, transient jaundice and respiratory distress of the newborn.

**Investigation**

Initial investigation included general baseline bloods but focused on the assessment of DSD. Over the first 4 weeks, exploration of absent red reflex and detection of microscopic haematuria then led to subsequent investigations.

Baseline blood tests were normal except for minimally elevated corrected calcium (2.85, NR: 1.9–2.8 mmol/L), elevated alkaline phosphatase (135, NR: 36–100 IU/L), leukopaenia (3.49, NR: 10–26×10⁹/L) and thrombocytopaenia (93, NR: 150–400×10⁹/L).

Early endocrine assessments included karyotype 46XY, ultrasound pelvis that showed no evidence of Müllerian structures or gonadal tissue and serum hormone assessments at 72 h of age: serum testosterone: 6.4 nmol/L, LH <0.5 IU/L, FSH <0.5 IU/L, DHEAS: 6.9 µmol/L and 17-hydroxy progesterone: 5.2 nmol/L. Testosterone measurements were performed using immunoassay.

Hormonal stimulation tests were undertaken on Day 14 to explore the hypothalamic-pituitary–gonadal axis (Table 1). The gonadotropin-releasing hormone (GnRH) stimulation test protocol involved sampling baseline luteinising hormone (LH) and follicle-stimulating hormone (FSH) followed by intravenous administration of gonadorelin hydrochloride 2.5 µg/kg with repeat LH and FSH sampling after 20 and 60 min. Results showed significantly raised LH (45.4 IU/L) at baseline (contrasting with the Day 3 undetectable level), with a 20% increase on stimulation, contrasting with the much lower baseline FSH (4.3 IU/L) with no appreciable increase after GnRH administration. The human chorionic gonadotropin (HCG) stimulation test protocol involved baseline serum testosterone then intramuscular administration of chorionic gonadotropin human (Pregnyl, Merck Sharp and Dome Ltd) 500 units daily for 3 days with repeat serum testosterone measurement 24 h after the last administration. The HCG test produced acceptable 50% increase in testosterone levels from baseline. In view of the unusual GnRH test profile, the GnRH and HCG tests were repeated aged 11 months (Table 1).

Renal abnormalities were identified: elevated calcium:creatinine ratio 2.08 mol/mol (normal <0.80),

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Initial tests aged 2 weeks were gonadotropin-releasing hormone (GnRH) stimulation test examining luteinising hormone (LH) and follicle-stimulating hormone (FSH) level followed by human chorionic gonadotropin (HCG) stimulation testing of serum testosterone. Both GnRH and HCG tests were repeated at age 11 months. *Baseline.
elevated protein:creatinine ratio 589 mg/mmol (normal <30) and generalised aminoaciduria. Renal ultrasound was normal. Alkaline phosphatase elevation persisted; serum phosphate was initially normal; however, levels reduced by 5 months of age (1.22, NR: 1.3–2.4 mmol/L), as did bicarbonate (20, NR: 22–29 mmol/L).

Several differential diagnoses were explored for the bilateral impalpable testes accompanied by additional system disorders and dysmorphism. Metabolic investigations excluded galactosaemia, Smith Lemli-Opitz syndrome, peroxisomal disorders and congenital disorders of glycosylation.

**Treatment**

Bilateral cataracts were confirmed at 8 weeks and bilateral cataract extractions with intraocular lens implants performed.

By 12 months, testes were palpable at the superficial inguinal ring, although surgery for left orchidopexy was required and undertaken at 16 months.

Management of renal tubulopathy involves renal replacement therapy with alfacalcidol, phosphate supplements, potassium citrate and sodium bicarbonate.

**Outcome and follow-up**

The constellation of cataracts, renal tubular acidosis, hypotonia and undescended testes was suggestive of Lowe syndrome. DNA sequencing identified a hemizygous mutation OCRL c.2409_2410delCT in exon 22. This frameshift mutation provided genetic confirmation of Lowe syndrome. The mother's mutational analysis was normal, demonstrating a de novo mutation rather than the more common X-linked mode of inheritance.

Now aged 5 years, the patient’s clinical problems include seizures, controlled on anticonvulsants, poor linear growth, which improved with percutaneous endoscopic gastrostomy feeding and constipation. There have been further recent problems with poor weight gain, hypernatraemic dehydration and hospitalisation for periods of stabilisation and broader care issues.

A potential third HCG stimulation test is considered; but the current clinical priorities of electrolyte and weight stabilisation have taken precedence with HCG test deferred at present. Recognition of the presence of HPG axis abnormalities suggestive of impaired testicular function has flagged the need to monitor this as an active issue in the years ahead.

**Discussion**

The few previous reports on endocrine abnormalities in Lowe syndrome have focused on abnormalities in adolescence and young adulthood including two with pubertal delay (5) and two with infertility (4). The clinical endocrine abnormality in our case was bilateral impalpable testes; two papers identify seven cases of cryptorchidism in Lowe syndrome (5, 6), but do not specify whether they were undescended but palpable or impalpable testes.

Also hypothalamic–pituitary–gonadal axis function in Lowe syndrome has not previously been described in neonates and infants. The Day 14 gonadotropin-releasing hormone stimulation (GnRH) test showed a striking increase in LH at baseline and on stimulation. Firstly, this result contrasted markedly with the undetectable initial gonadotropin levels at 72 h of age. Such discrepancy could potentially be explained by the suppressive effect of placental oestrogens in the first few days of life, although the rise over 11 days is marked. Secondly, this baby’s GnRH test was unusual in showing solely LH elevation unaccompanied by any FSH abnormalities.

A GnRH stimulation test forms part of the diagnostic work up of babies with ambiguous genitalia or impalpable testes in many expert paediatric endocrine centres to identify hypogonadotrophic hypogonadism. There is no universal agreement on its role as others have expressed the view that the GnRH stimulation test is of limited value (7). However, in our view, the marked LH elevation provided prognostic information on HPG axis abnormalities and hence was useful. The main unusual finding was the discrepancy between LH and FSH values. Raised levels of both LH and FSH would have been consistent with hypergonadotrophic hypogonadism. The LH elevation in our case was interpreted as due to the abnormal testicular development and descent. The literature around this hypothesis is conflicting. Other reports in infancy indicate that FSH is more significantly raised than LH (in 3-month-old males with cryptorchidism (8)), yet in adulthood LH elevation is the more prominent (in previously cryptorchid adult men (9)). The raised LH could reflect impaired Leydig cell function (8). Mouse studies have shown reduced Leydig cell activity in cryptorchidism, further implicating the LH–Leydig cell axis (10).

Other causes of isolated LH elevation were considered and excluded. Isolated LH elevation has been reported in complete androgen insensitivity syndrome (11), but here, the clinical features and serum testosterone were not supportive of this differential diagnosis.
LH elevation can indicate a testosterone biosynthetic defect, but testosterone baseline levels and increase on HCG stimulation were normal.

If the marked LH elevation and further rise on the GnRH was indicative of testicular failure, it seemed odd that the ensuing HCG stimulation test normal results suggested normal testicular function. In view of these discordant results, a repeat GnRH test was planned. Additional rationale for the repeat GnRH test was to explore the possibility of an LH receptor mutation, which would thus inform whether to pursue this genetic avenue.

Unfortunately, clinical factors postponed the repeat GnRH test beyond the preferred 4- to 6-month life window. It is possible that undetectable baseline and much lower stimulated LH and FSH levels are normal for 11 months of age due to the normal hypothalamic-pituitary-gonadal suppression generally present beyond 6 months until reactivation at puberty. However, they are more significant in this case due to their remarkable contrast with the earlier degree of LH elevation. Viewed in isolation, the second GnRH test shows peak LH 9.2IU/L at 60min to be higher than expected for age; absence of accompanying FSH elevation or clinical changes of puberty suggested this did not meet pubertal criteria. Instead, it is in keeping with the earlier LH elevation, but assumedly lower due to the impact of HPG axis suppression by this age. Comparing and contrasting the initial and repeat GnRH tests also indicates the value of considering the integrated picture rather than relying solely on individual tests. The first HCG stimulation test suggested acceptable testosterone levels, whereas the repeat showed a poor response. This discrepancy highlights shortcomings of testosterone immunoassay methodology in the neonatal period: cross-reactivity with foetal adrenal zone steroids could have erroneously elevated the first HCG stimulation testosterone ‘levels’. Our laboratory continues with samples for confirmation by tandem mass spectrometry. Awareness of assay methodology is important in DSD case management.

The summation of all the tests was that the markedly isolated LH elevation and poor testosterone response on repeat HCG indicates impaired testicular function and that testicular failure is a possible clinical problem in the next decade of life. Lowe syndrome is a chronic debilitating condition whose central features are renal, ophthalmological and neurological disease, with clinical management focused on these. Through advances in renal replacement therapy improving patient survival in Lowe syndrome, more boys are likely to reach adolescence. This case report illustrates less frequently appreciated gonadal axis abnormalities, suggesting that testicular function and descent may be affected before birth. Early testing of the HPG axis may contribute to earlier identification of testicular abnormalities. Improved awareness may facilitate early orchidopexy and enhance case management through adolescence with close pubertal monitoring and timely testosterone replacement minimising adverse growth and skeletal effects of delayed or absent puberty which would be beneficial in this patient group.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent
Written informed consent has been obtained from the patient's guardian for publication of the article.

Author contribution statement
C P B conceived the design of the work; B W undertook data collection and drafted the article; B W and C P B undertook data analysis and interpretation; C P B and C D I undertook critical revision of the article; B W, C D I and C P B gave final approval of the version to be published.

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