Is it time to commence newborn screening for congenital adrenal hyperplasia in Australia?

Summary

- 21-Hydroxylase deficiency (21-OHD) is the most common cause of congenital adrenal hyperplasia, with an incidence of 1:14 000 live births and equal prevalence among males and females.
- Newborns with the most severe "salt-wasting" form of 21-OHD are susceptible to salt-wasting crises in the first few weeks of life. This is associated with morbidity and mortality.
- 21-OHD newborn screening (NBS) is currently performed in many countries.
- Despite several prominent medical societies recommending 21-OHD NBS, no state in Australia currently screens for this condition.
- We report a case that illustrates the need to reconsider including 21-OHD in NBS.
- 21-OHD NBS can be reliable, sensitive and effective in reducing morbidity and mortality.

The most common cause of congenital adrenal hyperplasia (CAH) is 21-hydroxylase deficiency (21-OHD), a group of autosomal recessive conditions that impair cortisol production.[1,2] 21-OHD has an overall incidence of 1 : 14 000 live births, with equal prevalence among males and females.[2] The variable residual 21-hydroxylase enzyme activity in this condition causes a spectrum of clinical phenotypes, ranging from the most severe "classic" forms to the "non-classic" forms. The classic forms include the salt-wasting and simple virilising varieties. Two-thirds of patients with classic 21-OHD have salt wasting, and the remaining one-third have the simple virilising phenotype.[1]

In 21-OHD, the precursors, progesterone and 17-hydroxyprogesterone (17-OHP), accumulate to varying amounts and divert to androgen biosynthesis. Infant girls with classic CAH have ambiguous external genitalia, but boys appear normal.[1] Salt wasting due to lack of aldosterone usually occurs between 1 and 3 weeks after birth.[3,4] As the symptoms are non-specific, a correct diagnosis is often delayed. Thus, males with classic CAH are at serious risk of morbidity and mortality.[1,2]

Morbidity and mortality from CAH would be significantly reduced by the introduction of newborn screening (NBS) for 21-OHD. 21-OHD NBS has a specificity of greater than 99%, with sensitivity ranging from 92% to 100%.[5] Most countries offering 21-OHD NBS use the time-resolved, dissociation-enhanced, lanthanide fluorescence immunoassay (DELFIA).[6] 21-OHD NBS was first performed in Alaska in 1977, and, despite the recommendation of prominent medical societies,[7-10] no state in Australia performs 21-OHD NBS. We report a case illustrating the need for inclusion of 21-OHD in the NBS programs in Australia.

Case report: a baby boy with 21-OHD

A 21-day-old male infant of Polynesian background presented to his general practitioner with a 24-hour history of lethargy and poor feeding. There was no history of vomiting, diarrhoea, cough or fever. During ambulance transfer he went into cardiac arrest and required resuscitation. Defibrillation and intubation were needed immediately on arrival at the hospital. Results of initial blood testing showed a blood glucose level of 1.8 mmol/L (reference range [RR], 3.6–7.7 mmol/L); plasma sodium concentration, 122 mmol/L (RR, 130–149 mmol/L); potassium concentration, 8.2 mmol/L (RR, 4.0–7.0 mmol/L); chloride concentration, 105 mmol/L (RR, 105–115 mmol/L); bicarbonate concentration, 7 mmol/L (RR, 17–28 mmol/L); anion gap, 10 mmol/L (RR, 5–15 mmol/L); urea concentration, 19.6 mmol/L (RR, 0.2–4.0 mmol/L); creatinine level, 114 µmol/L (RR, 20–60 µmol/L); pH, 6.96 (RR, 7.35–7.45); partial pressure of carbon dioxide, 34 mmHg (RR, 27–40 mmHg); partial pressure of oxygen, 182 mmHg (RR, 80–110 mmHg); base excess, –23.4 mmol/L (RR, –7.0 to –1.0 mmol/L); and lactate concentration, 4.3 mmol/L (RR, 0.2–2.0 mmol/L). Initial treatment included intravenous inotropes, saline, albumin, dextrose, antibiotics, bicarbonate and hydrocortisone.

The patient had been born at term with a birthweight of 3.94 kg (between the 75th and 90th percentiles) after an uncomplicated antenatal period. At birth, there was meconium-stained liquor but his Apgar scores were 8 and 9 at 1 minute and 5 minutes, respectively. There was no significant family history and no consanguinity. He had bottle fed well until the 24 hours before presentation.

Examination findings were consistent with dehydration. He weighed 3.65 kg (between the 25th and 50th percentiles) and his anterior fontanelle was sunken. He was not hyperpigmented and had normal male external genitalia. The rest of the examination was unremarkable.

The first urine sodium concentration, taken 3 hours after presentation, was 92 mmol/L, with a concurrent plasma sodium concentration of 121 mmol/L. Additional investigation showed elevated levels of troponin, 0.34 µg/L (RR, < 0.05 µg/L); 17-OHP, 470 nmol/L (RR, < 7 nmol/L); renin, 73 000 mU/L (RR, < 500 mU/L); aldosterone, 10 680 pmol/L (RR, 50–5800 pmol/L); androstenedione, 74 nmol/L (RR, < 4.0 nmol/L); and testosterone, 5.70 nmol/L (RR, 0.03–6.14 nmol/L). Abdominal ultrasound showed marked bilateral adrenomegaly with structurally normal kidneys and urinary tract. Plasma sodium, potassium and creatinine levels normalised within 24 hours. A magnetic resonance imaging scan of the head 7 days after

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MJA 2011; 195: 260–262
doi: 10.5694/mja11.10284

presentation showed no evidence of hypoxic–ischaemic encephalopathy.

He remained in the paediatric intensive care unit for 2 days before being transferred to the ward; he was discharged 7 days after presentation on hydrocortisone, fludrocortisone and sodium chloride tablets. At 1-month follow-up, he was noted to be thriving. Genetic testing demonstrated homozygous mutation (c.293-13A/C>G) in the *CYP21A2* gene, which is associated with either a salt-wasting or a simple virilising CAH phenotype.

To screen or not to screen?

The aim of 21-OHD NBS is to reduce the morbidity (neurological damage or intellectual disability) and mortality associated with salt-losing crises.[3,6] Other benefits include shortening the time of sex assignment for babies with a virilised 46, XX karyotype, and avoiding precocious puberty and decreased final height in the simple virilising form. As mentioned above, boys generally appear normal at birth. They are thus unlikely to be diagnosed before discharge from hospital. Symptoms of salt wasting are non-specific and usually develop between 1 and 3 weeks after birth. NBS for 21-OHD would use the same blood spots that are currently collected for all newborns at 72 hours, making results available by the time babies are 10 days old.[3] This would be before most babies with salt-wasting 21-OHD became symptomatic, thus allowing time to institute appropriate replacement therapy with hydrocortisone and fludrocortisone. NBS for 21-OHD only identifies a few babies with non-classic CAH.[6]

NBS for 21-OHD has not been introduced in Australia. One reason for this is that there are currently no data available worldwide on the cost-effectiveness of screening for 21-OHD.[11-13] This is because the benefits of early detection are difficult to quantify. In one American study, it was estimated that screening for 21-OHD would cost slightly more than $20 000 per life-year (LY) saved. This is less than the $50 000 per LY saved conventionally used as a benchmark for cost-effectiveness.[14] Another American study put forward data suggesting that the cost is above $50 000 per LY saved. The authors noted, however, that, based on United States regulatory policy decisions, society is willing to spend up to $300 000 per LY saved.[15]

However, we do know the financial cost involved; a 2-year pilot study conducted in New South Wales and the Australian Capital Territory estimated that the within-laboratory cost per 21-OHD case detected, measuring 17-OHP using DELFIA, was $42 717.[3] This is comparable to the cost in other countries.[5,16,17] All these countries have advocated for 21-OHD NBS based on studies done several years after implementation. The Australian pilot study also concluded that there is good justification for 21-OHD NBS.[3]

The second argument against 21-OHD NBS is that insufficient data exist to prove a reduction in mortality and morbidity. Many studies have found, however, that the prevalence of CAH is higher in the screened populations than in unscreened populations comprising similar ethnic backgrounds. The unequal ratio of males to females in unscreened populations is consistent with an increased male neonatal mortality due to undetected salt-wasting 21-OHD CAH. This was even found in areas with good health care, where it was originally thought that patients with CAH would be clinically diagnosed in good time.[6,11,18-22] Studies have also found decreased hospitalisation and decreased time to correct sex assignment in the screened population.[5,17,21] The case we present also illustrates the serious and real mortality risk in baby boys with salt-wasting CAH.

The third argument against adopting 21-OHD NBS is the previously documented low positive predictive value (PPV) of screening methods. This is primarily due to the use of the DELFIA method, which has a PPV of 1%, resulting in many unnecessary follow-ups.[6] The number of false positives could be reduced by using cut-offs adjusted for weight and gestational age.[11] Immunoassay specificity can also be improved by organic solvent extraction.[10] New strategies in 21-OHD NBS include second-tier screening with either molecular testing or steroid analysis using liquid chromatography-tandem mass spectrometry (LC-MS/MS). Molecular testing is less reliable and more costly and time-consuming than steroid analysis by LC-MS/MS.[1,6] Moreover, LC-MS/MS is now more accessible in most NBS laboratories.[3,6] In a German program incorporating second-tier LC-MS/MS testing using the sum of 17-OHP and 21-deoxycortisol (a steroid produced by 11-β-hydroxylation of 17-OHP) levels divided by cortisol level, investigators achieved a PPV of 100%; they correctly identified 16 affected infants out of 242 500 infants tested, with no false-positive results.[23] Furthermore, the Newborn Screening Quality Assurance Program is available for 21-OHD NBS to ensure high standards of testing.[24]

The lack of a screening strategy in Australia is unusual, given that 21-OHD NBS is currently performed in many countries, including the US, New Zealand (for the past 28 years), Germany, Switzerland, Austria, France, Sweden, the Netherlands, Spain, Italy, Japan and Canada.[10,25] It appears to meet all population screening criteria.[13] That is, CAH results in high morbidity and mortality if undetected; the 21-OHD NBS test is reliable and efficient; there is effective cheap treatment for CAH; and the incidence of CAH is relatively high (similar to phenylketonuria).[7,16] The American College of Medical Genetics considers CAH to be one of the 29 conditions for which screening should be mandated.[8] The National Academy of Clinical Biochemistry in the US also strongly recommends CAH screening.[9] Recently, the US Endocrine Society Clinical Guidelines Subcommittee published a practice guidelines for CAH due to 21-OHD, and recommended that 21-OHD be included in all NBS programs.[10]

We ask the question: when will Australia introduce 21-OHD NBS? The case we report provides another reminder of the potential mortality associated with salt-wasting CAH in the neonatal period. With others, we have previously reported a case of CAH detected at autopsy.[4] As a means of reducing the neonatal mortality associated with salt-wasting 21-OHD, and given improvements in methodology and accumulated evidence, we suggest that now is the time for Australia to start NBS for 21-OHD.

Competing interests: No relevant disclosures.

Provenance: Not commissioned; externally peer reviewed.

1 Riepe FG, Sippell WG. Recent advances in diagnosis, treatment, and outcome of congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *Rev Endocr Metab Disord* 2007; 8: 349-363.
2 Ghayee HK, Auchus RJ. Basic concepts and recent developments in human steroid hormone biosynthesis. *Rev Endocr Metab Disord* 2007; 8: 289-300.
3 Gleeson HK, Wiley V, Wilcken B, et al. Two-year pilot study of newborn screening for congenital adrenal hyperplasia in New South Wales compared with nationwide case surveillance in Australia. *J Paediatr Child Health* 2008; 44: 554-559.
4 Gozzi TG, Harris NP, McGown IN, et al. Autopsy diagnosis of 21-hydroxylase deficiency CAH in a case of apparent SIDS. *Pediatr Dev Pathol* 2005; 8: 397-401.
5 Van der Kamp HJ, Noordam K, Elvers B, et al. Newborn screening for congenital adrenal hyperplasia in the Netherlands. *Pediatrics* 2001; 108: 1320-1324.
6 White PC. Neonatal screening for congenital adrenal hyperplasia. *Nat Rev Endocrinol* 2009; 5: 490-498.
7 Therrell BL. Congenital adrenal hyperplasia. *Endocrinol Metab Clin North Am* 2001; 30: 15-30.
8 Watson MS, Mann MY, Lloyd-Puryear MA, et al. Newborn screening: toward a uniform screening panel and system — executive summary. *Genet Med* 2006; 8: 1S-11S.
9 Dietzen DJ, Rinaldo P, Whitley RJ, et al. National Academy of Clinical Biochemistry Laboratory Medicine practice guidelines: follow-up testing for metabolic disease identified by expanded newborn screening using tandem mass spectrometry: executive summary. *Clin Chem* 2009; 55: 1615-1626.
10 Speiser PW, Azziz R, Baskin LS, et al. Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2010; 95: 4133-4160.
11 Brameld K. Congenital adrenal hyperplasia — the Australian perspective. Perth: Office of Population Health Genomics, Department of Health, Government of Western Australia, 2006. http://www.genomics.health.wa.gov.au/publications/docs/Congenital_Adrenal_Hyperplasia.pdf (accessed Aug 2011).
12 Brameld K. Framework for adding new tests for conditions within the Newborn Screening Protocol. Perth: Office of Population Health Genomics, Department of Health, Government of Western Australia, 2006. http://www.genomics.health.wa.gov.au/publications/docs/Newborn_Screening_Framework.pdf (accessed Aug 2011).
13 Human Genetics Society of Australasia, Royal Australasian College of Physicians. Newborn blood spot screening [policy statement]. Sydney: RACP, 2004. http://69.72.135.23/website/wp-content/uploads/2009/12/2004-P01.pdf (accessed Dec 2010).
14 Carroll AE, Downs SM. Comprehensive cost–utility analysis of newborn screening strategies. *Pediatrics* 2006; 117: S287-S295.
15 Yoo BK, Grosse SD. The cost effectiveness of screening newborns for congenital adrenal hyperplasia. *Public Health Genomics* 2009; 12: 67-72.
16 Thil'en A, Nordenström A, Hagenfeldt L, et al. Benefits of neonatal screening for congenital adrenal hyperplasia (21-hydroxylase deficiency) in Sweden. *Pediatrics* 1998; 101 (4): e11.
17 Brosnan CA, Brosnan P, Therrell BL, et al. A comparative cost analysis of newborn screening for classic congenital adrenal hyperplasia in Texas. *Public Health Rep* 1998; 113: 170-178.
18 Speiser PW. Prenatal and neonatal diagnosis and treatment of congenital adrenal hyperplasia. *Horm Res* 2007; 68: 90-92.
19 Grosse S, Vliet GV. How many deaths can be prevented by newborn screening for congenital adrenal hyperplasia? *Horm Res* 2007; 67: 284-291.
20 van der Kamp HJ, Wit JM. Neonatal screening for congenital adrenal hyperplasia. *Eur J Endocrinol* 2004; 151: U71-U75.
21 Brosnan PG, Brosnan CA, Kemp SF, et al. Effect of newborn screening for newborn screening for congenital adrenal hyperplasia. *Arch Pediatr Adolesc Med* 1999; 153: 1272-1278.
22 Balsamo A, Cacciari E, Piazzi S, et al. Congenital adrenal hyperplasia: neonatal mass screening compared with clinical diagnosis only in the Emilia–Romagna region of Italy, 1980–1995. *Pediatrics* 1996; 98: 362-367.
23 Janzen N, Peter M, Sander S, et al. Newborn screening for congenital adrenal hyperplasia: additional steroid profile using liquid chromatography-tandem mass spectrometry. *J Clin Endocrinol Metab* 2007; 92: 2581-2589.
24 De Jesús VR, Simms DA, Schiffer J, et al. Pilot proficiency testing study for second tier congenital adrenal hyperplasia newborn screening. *Clin Chim Acta* 2010; 411: 1684-1687.
25 Screening Matters. Newsletter of the National Screening Unit. 2006; Mar. http://www.nsu.govt.nz/files/NSU/issue_6.pdf (accessed Jul 2011). ❑