

Office of Population Health Genomics

Paper:
Congenital Adrenal Hyperplasia -
the Australian perspective

Purpose: To provide a perspective on congenital adrenal hyperplasia in Australia with a view to consideration of adding this test to the recommended newborn screening protocols.

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Congenital Adrenal Hyperplasia – the Australian perspective

Congenital adrenal hyperplasia (CAH) is the term applied to a group of autosomal recessive endocrine disorders of adrenal steroid biosynthesis. Mutations in the CYP21 gene, which encodes for the enzyme 21-hydroxylase (21OH), are the most common cause of CAH, accounting for more than 90% of cases. The incidence in most populations ranges from approximately 1:10,000 to 1:18,000, with a similar prevalence between males and females. Classical CAH often presents as a simple virilizing form (SV), causing ambiguous genitalia in females, or as a salt wasting form (SW), with vomiting and dehydration in the neonatal period. The SW form is more common, accounting for around 70% of cases. The non-classic or late onset form of CAH is unlikely to be detected phenotypically or by screening for elevated 17-hydroxyprogesterone levels in the newborn.

The longer term effects of CAH include precocious puberty and advanced bone and height age. However, premature closure of the epiphyseal plates then results in permanent short stature. There is mixed evidence as to whether early treatment improves height outcome. Precocious puberty is more likely to develop when the diagnosis of CAH is delayed or with poor control of adrenal androgen secretion.¹

Epidemiology of CAH in Australia

The incidence of CAH in WA is 1:11,111 births as determined by cases diagnosed between 1980 – 2005 (55 cases). The male to female ratio is 22:32 (0.7: 1). Twenty-nine out of fifty-one cases (57%) were diagnosed within 7 days (4 diagnosed antenatally). (Data provided by Prof Carol Bower of the WA Birth Defect Registry).

Linkage of WA Birth Defect Registry Data to the WA Hospital Morbidity Data System show that over the period 1980-2000 there were an average of 2.7 admissions per child with CAH during the first year of life with a mean length of stay of 4.9 days and a median of 3.0 days. Forty-two of the 85 admissions had a principal diagnosis of “Disorder of the adrenal glands” and were possibly associated with an adrenal crisis that may have been avoided by screening. The length of stay for these admissions was longer than that for all admissions, mean 7.5 days and median 5.0 days. (Personnal communication - Lynn Colvin, Carol Bower).

Costs of these admissions can be estimated at around \$7638 per admission with complications and \$2691 per admission without complications. (2002 Cost weight for DRG K64A – Endocrine disorders with severe complications and DRG K64B Endocrine disorder with no complication).

A national study conducted between October 1995 and September 1997 by the Australian Paediatric Surveillance Unit found an incidence of 1: 16,949 (29 cases) and a male:female ratio of 13:16 (0.8:1). In NSW and ACT where a pilot screening program was operated, 6 out of 12 newborns were initially detected by screening. It concluded that national newborn screening would not be introduced until cheaper technology (which was under development at that time) was available.²

Official data are not collected in Victoria, but the incidence of presentation to the Royal Children’s Hospital in Parkville was 1:16,400 during 1969-1993.^{3,4}

Outcome

Australian data are available from a retrospective Victorian study based on 97 (50 males, 47 females) patients diagnosed between 1969 and 1993 at the Royal Children's Hospital in Melbourne.³ Five females were excluded from the study as they were only admitted for genital surgery and a further two males and one female as their medical records were not available. Of the remaining 89 patients:

- 32 (36%) were males presenting with salt loss in infancy;
- 34 (38%) were females presenting with ambiguous genitalia;
- 10 (11%) were males presenting with precocious virilization after infancy;
- 7 (8%) were females presenting with signs of androgen excess after infancy; and
- 6 (7%) were asymptomatic males diagnosed as a result of affected siblings.

Of the 32 males with salt loss in infancy, the age of diagnosis was available for 30 of them. Eleven were diagnosed in their second week of life, 8 in the third week, 6 in the fourth week and 5 after the fourth week. Hyperkalaemia with cardiac toxicity was common in those who presented early. For the others, sepsis and pyloric stenosis were common differential diagnoses at the time of admission.

In 29 of the 34 females, CAH was diagnosed and treated in early infancy. However, one presented with a salt-losing crisis in the fifth week of life and it was only at that stage that ambiguous genitalia became apparent. Five females had delayed diagnosis and treatment.

The ten males with precocious virilization presented at a mean age of 4.1 +/- 1.7 years with premature sexual maturation and bone age in advance of chronological age.

The seven girls with mild virilization were diagnosed at ages between 3 and 7.5 years. Their bone age was advanced by varying degrees.

Of these patients, eleven had a total of sixteen documented hospitalizations for adrenal crisis. Two patients died aged 3 and 5. The cause of death was uncertain, but adrenal crisis was likely.

These data suggests that the introduction of CAH screening would enable earlier diagnosis and improve the long-term outcome for people with CAH. However, it is likely that the diagnosis of CAH has improved in recent years.

Screening options

Simple and robust assays based on 17OHP measurement are now commercially available with an achievable false-positive rate of less than 0.2% (mostly low birth weight and premature infants). Composite data from around the world indicate that false-negatives comprised 15 missed cases – 1 in 420,000 (eight with salt wasting, four of which were missed due to human error, one simple virilizing and six with mild late-onset disease) out of 6.29 million infants screened, compared with 409 (1 in 15,400) cases of CAH detected.⁵ The problem of false-positives with premature/low birth weight infants can successfully be overcome by using a different measurement range for these infants provided that birth weight/prematurity data are accurately entered on the blood-spot screening card. In cases of late-onset disease the 17OHP values overlap the normal range, but the ACTH stimulation test (60 minutes) appears successfully to identify patients with CAH.⁶

There are currently no data available in Australia on the cost-effectiveness of screening for CAH. A Swedish study estimated the cost at \$53 400 (US) per patient diagnosed earlier because of screening or \$26 700 per patient including follow-up and mutation analysis.⁷ A US study estimated the cost per diagnosis as \$115, 169 for a single screen, based on the US dollar in 1994.⁸ A pilot screening program would enable cost data to be collected and the feasibility of CAH screening in Australia to be assessed. A mechanism for evaluating the program is required. At its most simple, this could comprise collection of the following information:

- type of CAH;
- age at diagnosis;
- number of hospital admissions and length of stay within the first year of life and subsequent to birth;
- number of ICU admissions and length of stay in ICU within the first year of life and subsequent to birth;
- death.

This information needs to be collected both pre and post screening. Where possible, the pre-screening data could be collected retrospectively from medical records. As noted by Kelnar, “a prospective study which aims to (1) assess physical, psychometric, psychological and psychosexual functioning in patients and families, and (2) prospectively evaluate neonatal screening in reducing morbidity and preventing mortality would be highly desirable.”⁹ An Australian CAH trial should be able to achieve the second of these objectives.

Screening for Congenital Adrenal Hyperplasia (CAH) in Australia

The evidence for adding CAH to a Newborn screening protocol has been reviewed in the UK^{10 11} and the USA¹². The UK screening policy currently recommends against screening for CAH¹³ although the report by Seymour et al suggested there was sufficient evidence to introduce this program. The US report ranked potential conditions to be screened in newborns according to a value determined by a panel of experts and review of the literature. The result of this process was that the US Newborn Screening Program should include CAH.

Evidence for assessing the suitability of CAH for the newborn screening program is provided in the Appendices and it appears to fulfill most criteria although in some cases the evidence is limited. The difficulty in determining the suitability of CAH for newborn screening results from the difficulty in determining whether screening will lead to earlier identification than clinical diagnosis. Evidence in favor of earlier identification due to screening comes from studies that show a higher prevalence of CAH resulting from screening. Unequal ratios of males to females also indicate that some diagnoses are being missed. However, such data as are available in Australia indicates that the prevalence of CAH is comparable to that seen in countries where screening is undertaken and no significant difference has been seen between the numbers of males and females. Screening should result in the aversion of adrenal crisis and related morbidity and mortality but limited data are currently available.

It is proposed that a pilot newborn screening program for CAH be conducted across Australia. This needs to be accompanied by data collection on the number of cases of CAH and morbidity and mortality associated with adrenal crisis, both pre- and post-screening in order to evaluate its effectiveness.

Cost Schedule

	No. of Births 2004	CAH reagent cost, \$ (\$1.60 per baby)	Equipment, \$	Personnel
NSW	85894	137,430.40	500,000	
Vic	62417	99,867.20		
Qld	49940	79,904.00		
SA	17140	27,424.00		
WA	25295	40,472.00		1FTE @ \$60k
Tas	5809	9,294.40		
NT	3551	5,681.60		
ACT	4174	6,678.40		
Aus	254246	406,793.60		

Potential Cost Recovery

	Rate	Cost of treatment
Hospitalisation	20 per 250,000 births	$((\$2691 * 3) + (\$7638)) * 5 = \$78,555$
Disability	1 per 250,000 births	\$80,000 - \$400,000
Mortality	-	\$0
Total		\$158,555 - \$478,555

Hospitalisation - assume 1 in 4 admissions has severe complications
 2002 Cost weight for DRG K64A - Endocrine disorders with severe complications
 2002 Cost weight for DRG K64B - Endocrine disorder with no complication

Disability data - personal communication - Dr E. Geelhoed, Health Economist, The University of Western Australia

Screening Framework For Congenital Adrenal Hyperplasia

See

The Condition	
1. The condition should be an important health problem	Incidence of 1 in 5000 to 1 in 21,270 detected by screening and serious consequences if untreated ¹⁴
2. The epidemiology and natural history should be well understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage.	Range of disorders recognized with different clinical outcomes. Detectable by measurement of 17-OHP concentration in the blood. ¹⁴
3. All the cost-effective primary prevention interventions should have been implemented as far as practicable.	Not relevant
4. If carriers of a mutation are identified as a result of screening the natural history of people with this disease, this status should be understood, including the psychological implications.	Carriers not detected with the 17-OHP test
The Test	
5. There should be a simple, safe, precise and validated screening test	Measurement of 17-OHP concentration in blood ¹⁴
6. The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed	Cut-off values are determined by the system established to manage “screen positive” results eg MSMS, acceptable FPR & recall rate.
7. The test should be acceptable to the population	YES – part of newborn screening suite
8. There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals.	Treatment options documented ¹⁵
9. If the test is for mutations the criteria used to select the subset of mutations to be covered by screening, if all possible mutations are not being tested, should be clearly set out.	Not relevant
The Treatment	
10. There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment.	YES ^{16 17 18} {Donaldson, 1994 #51 19 20}
11. There should be agreed evidence based policies covering which individuals should be offered treatment and the appropriate treatment to be offered.	YES ¹⁵
12. Clinical management of the condition and patient outcomes should be optimized in all health care providers prior to participation in a screening programme.	¹⁵
The Screening Programme	
13. There should be evidence from high quality Randomised Controlled Trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an ‘informed choice’ (eg Down’s syndrome) there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.	All data are from cohort studies. ⁵ Control populations consist of the same population over a different time period or a comparable population from a different geographic area. Evidence for effectiveness of screening programme is based on higher incidence rates in screened versus non-screened populations and unequal sex-ratio. Little evidence documenting reduction in morbidity/mortality
14. There should be evidence that the complete screening programme (test,	YES ²¹

diagnostic procedures, treatment/intervention) is clinically, socially and ethically acceptable to health professionals and the public.	
15. The benefit from the screening programmed should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment).	YES – require a community attitude study?
16. The opportunity cost of the screening programmed (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (ie value for money)	See below
17. There should be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards	Principles and guidelines under development.
18. Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be available prior to the commencement of the screening programme	Approximate costs: Reagent \$1.60 per baby screened.
19. All other options for managing the condition should have been considered (eg improving treatment, providing other services), to ensure that no more cost effective intervention could be introduced or current interventions increased within the resources available.	Not relevant
20. Evidence-based information, explaining the consequences of testing, investigation and treatment, should be made available to potential participants to assist them in making an informed choice.	To be developed
21. Public pressure for widening the eligibility criteria for reducing the screening interval and for increasing the sensitivity of the testing process, should be anticipated. Decisions about these parameters should be scientifically justifiable to the public.	Not relevant
22. If screening is for a mutation the programme should be acceptable to people identified as carriers and to other family members.	Not relevant

US Screening Evaluation

See: <http://mchb.hrsa.gov/screening/>

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