Original articles

Should we screen for congenital adrenal hyperplasia? A review of 117 cases

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SUMMARY A total of 117 patients with congenital adrenal hyperplasia who were under the care of paediatricians at Birmingham Children's Hospital between 1958 and 1985 were reviewed retrospectively. There were 47 boys (40%) and 70 girls (60%); 30 of the 47 boys (64%) and 38 of the girls (58% of the 66 whose salt state was known) were salt losers. In all salt losers the condition was diagnosed before the age of 6 months, 90% of the diagnoses being made during the first month. The ratio of boys to girls, the distributions of salt losers to non-salt losers, and the age at diagnosis were studied in relation to the year of birth. Early diagnosis was found to be more common in children born after 1970 due partly to the introduction of a method of assaying the concentration of 17α-hydroxyprogesterone in serum, partly to an increase in the number of paediatricians in the West Midlands, and partly to the appointment of a paediatric endocrinologist. A neonatal screening programme does not seem to be necessary.

Congenital adrenal hyperplasia most commonly results from a deficiency of 21-hydroxylase, an enzyme required for the production of both cortisol and aldosterone. The prevalence varies between 1 in 490 in Alaskan Yupik Eskimos and 1 in 67 000 in Maryland in the United States. In Western Europe estimates range from 1 in 5000 to 1 in 13 000 in a series of case reports and 1 in 5000 to 1 in 18 000 from neonatal screening. Up to two thirds of cases are of the salt losing variety, which usually presents in the neonatal period with symptoms of vomiting, diarrhoea, and failure to thrive; if it is not diagnosed and treated early the infant may die.

In 1981 a committee of experts reported to the Council of Europe and recommended mass screening for this condition as soon as a suitable assay became available. Adrenal hyperplasia due to 21-hydroxylase deficiency is diagnosed when blood concentrations of 71α-hydroxyprogesterone (17-OHP) are grossly raised, and microassays suitable for mass neonatal screening using capillary blood have been reported. There is, however, disagreement over the desirability of neonatal screening for this disease, and there is no unified policy. Several pilot studies have been undertaken but no consensus has emerged. The purpose of this study was to review retrospectively patients with congenital adrenal hyperplasia under the care of paediatricians at the Children's Hospital, Birmingham, as part of our assessment of the need for a neonatal screening programme in this region.

Patients

We studied all patients known to have congenital adrenal hyperplasia who were admitted to the Children's Hospital between 1958 and 1985. Information collected included the patient's date of birth, sex, diagnosis (salt losing or non-salt losing), age at diagnosis, presenting features, and relevant family history. Most patients (102; 87%) were from within the West Midlands region. The ethnic origin was not known in all cases, although at least six were from Asian families. These included three genetic boys (all salt losers) with 3β-hydroxysteroid dehydrogenase (3β-HSD) deficiency who presented at birth with severe hypospadias and incomplete masculinisation. Two of these were siblings whose parents were first cousins. There were no other cases of consanguinity. One non-salt losing girl who presented at birth with ambiguous genitalia was diagnosed as having 11β-hydroxylase deficiency. The remaining patients were believed to have 21-hydroxylase deficiency, either on the basis of results of adrenocorticotrophic hormone stimulation tests as described by Galal or, in more recent cases, because of an increased serum 17-OHP concentration. Classification of salt losers was by both clinical and biochemical evidence of salt loss.
Results

We studied 117 patients; in some cases not all the information was available. The patients comprised 47 boys (40%) and 70 girls (60%), the male to female ratio being 2:3. Thirty of the 47 boys (64%) and 38 of 66 girls (58%) were salt losers.

Data from three boys with 3β-HSD deficiency were excluded because they were not comparable with the data from the boys with 21-hydroxylase deficiency. The Figure shows the ages at diagnosis. The condition was diagnosed in half of the girls within 24 hours of birth by the presence of ambiguous external genitalia. In all salt losers the condition was diagnosed by the age of 6 months, in 90% during the first month.

The age at diagnosis was studied with reference to the year of birth. There seemed to be an improvement in the speed of diagnosis in patients born in the 1970s compared with those born previously. To investigate this we divided the patients into two groups: those born before 1970 (group 1) and those born during 1970-85 (group 2). The diagnosis was made earlier in group 2 compared with group 1, as shown by the significantly lower mean age at diagnosis (p<0.01) and the higher proportion of children in whom the condition was diagnosed by 1 month of age (Table 1). Table 2 shows the distribution of sex and salt loss in the two groups.

Table 1  Age at diagnosis related to year of birth

<table>
<thead>
<tr>
<th></th>
<th>Born before 1970 (n=61)</th>
<th>Born during 1970-85 (n=46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (months) at diagnosis</td>
<td>21.3 (33)</td>
<td>5.4 (48)</td>
</tr>
<tr>
<td>No (%) aged less than 1 month</td>
<td>33 (54)</td>
<td>34 (74)</td>
</tr>
<tr>
<td>Boys</td>
<td>8 (13)</td>
<td>12 (26)</td>
</tr>
<tr>
<td>Girls</td>
<td>25 (41)</td>
<td>22 (46)</td>
</tr>
<tr>
<td>No (%) aged less than 1 year</td>
<td>43 (71)</td>
<td>39 (85)</td>
</tr>
<tr>
<td>Boys</td>
<td>12 (20)</td>
<td>15 (33)</td>
</tr>
<tr>
<td>Girls</td>
<td>31 (51)</td>
<td>24 (52)</td>
</tr>
</tbody>
</table>
The consequences established in Discussion the age older sibling whether non-salt loser period older sibling diagnosis groups. In compared with studied. patients proportion of salt losers proportion of the 3 Presentation of condition in boys and girls Table 2 Proportions of salt losers by sex and year of birth

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Boys</th>
<th>Girls</th>
<th>Male:female ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>68/117* (60)</td>
<td>33/66 (50)</td>
<td>35/47 (75)</td>
<td>1:1.4</td>
</tr>
<tr>
<td>Born before 1970 (group 1)</td>
<td>30/47 (64)</td>
<td>14/25 (56)</td>
<td>16/22 (73)</td>
<td>1:1.1</td>
</tr>
<tr>
<td>Born during 1970-85 (group 2)</td>
<td>38/70* (58)</td>
<td>19/41 (46)</td>
<td>19/25 (76)</td>
<td>1:1.6</td>
</tr>
</tbody>
</table>

*Diagnosis was not known in four cases.

Table 3 Presentation of condition in boys and girls (information not available for two salt losers and one non-salt loser)

<table>
<thead>
<tr>
<th></th>
<th>Salt losers</th>
<th>Non-salt losers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Girls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No in group</td>
<td>38</td>
<td>28</td>
</tr>
<tr>
<td>No with:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ambiguous genitalia</td>
<td>38</td>
<td>28</td>
</tr>
<tr>
<td>Adrenal crisis or hyponatraemia</td>
<td>2*</td>
<td>2</td>
</tr>
<tr>
<td>Vomiting or failure to thrive</td>
<td>6</td>
<td>2*</td>
</tr>
<tr>
<td>Precocious puberty</td>
<td>—</td>
<td>6</td>
</tr>
<tr>
<td>Boys</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No in group</td>
<td>30</td>
<td>17</td>
</tr>
<tr>
<td>No with:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adrenal crisis</td>
<td>2</td>
<td>—</td>
</tr>
<tr>
<td>Hyponatraemia or dehydration</td>
<td>5</td>
<td>—</td>
</tr>
<tr>
<td>Feeding problems or failure to thrive or vomiting</td>
<td>18</td>
<td>—</td>
</tr>
<tr>
<td>Ambiguous genitalia</td>
<td>3†</td>
<td>—</td>
</tr>
<tr>
<td>Precocious puberty</td>
<td>—</td>
<td>15</td>
</tr>
<tr>
<td>Comatose</td>
<td>—</td>
<td>1</td>
</tr>
</tbody>
</table>

*Two designated male at birth.
†All with 3β-HSD deficiency.

The proportion of salt losers was increased in group 2 compared with group 1 (p<0.01). In group 2 a lesser proportion of the patients were boys, although the difference in the male to female ratios between the two groups was not significant (p>0.1).

Table 3 shows the presenting features of the patients studied.

Nineteen families yielded several cases, the diagnosis being the same for each. In eight cases knowledge of an older affected sibling led to earlier diagnosis. In the remaining cases (all girls) with an older sibling diagnosis was made in the neonatal period due to ambiguous genitalia, and we cannot say whether knowledge of adrenal hyperplasia in the older sibling had any effect on the diagnosis. One female non-salt loser born in 1949 was diagnosed at the age of 10 only after the diagnosis had been established in her younger sister aged 3.

Discussion

The consequences of delayed diagnosis of congenital adrenal hyperplasia are well known, and for these reasons neonatal screening has been advocated. Others have suggested that the condition is easily diagnosed in the neonatal period and there is no need for neonatal screening. As part of our assessment of the need for a screening programme in Birmingham we reviewed patients with congenital adrenal hyperplasia who had attended Birmingham Children’s Hospital over 27 years. We chose to study the data with respect to the year of birth, and 1970 was important for several reasons: assays for 17-OHP became available then for the first time in this region, the number of paediatricians increased, and the appointment of a paediatric endocrinologist made the disease a major interest in the region.

For an autosomal recessively inherited disorder the expected male to female ratio is 1:1. In our study the overall ratio was 2:3, but when the year of birth was taken into account we found that, for children born in 1970 onwards, the ratio was closer to the expected 1:1. Furthermore, the prevalence of salt loss when related to the year of birth was significantly higher for children born in 1970 onwards. Although the numbers in our groups were small, these findings may suggest that there were fewer unidentified deaths among salt losing boys born after 1970. We are aware that during the period of this study two deaths occurred at Birmingham Children’s Hospital for which findings at necropsy were consistent with adrenal hyperplasia. Both infants were boys, born in 1962, who died at 20 days and 4 weeks of age, respectively. The pattern of referral may, however, have changed over the period of study, and more selective referral to the Children’s Hospital with fewer referrals of non-salt losing patients could have contributed to our findings.

Although in girls the condition is often diagnosed in the newborn period, in this study only half of the diagnoses in girls were made within 24 hours of birth; in some cases the diagnosis was not made until the child approached her teens. In addition, four genetic females were assigned male sex at birth. We are not aware of any incorrect assignments of sex after 1971, and all the girls in whom the diagnosis
was made late were born before 1970. Among the
girls born in 1970 onwards the condition was
diagnosed in all but one by 2.5 months (and in 92% 
within two weeks of birth), suggesting earlier di-
agnosis in recent years. Interestingly, detection in 
boys increased from 1970 onwards (Table 1). An
abnormality of the male genitalia at birth is not
easily discernible and therefore cannot explain this;
improved clinical awareness of electrolyte distur-
ances in male infants seems more likely.

We cannot provide data on the incidence of 
congenital adrenal hyperplasia in the West Midlands
as not all cases are referred to the Children's
Hospital and some patients may have died with the
condition undiagnosed. In addition, the immigrant
population changed over the period of our study,
and this may have had an effect on the incidence.
Rudd, however, looked at data over one year from
neonates born at eight major maternity units in the
West Midlands. There were 24 750 births, and
congenital adrenal hyperplasia was diagnosed in
four children (three girls and one boy), giving a
prevalence of 1 in 6188. This is much higher than the
figure quoted by Wallace et al in Scotland (1 in 18 401),
obtained by neonatal screening and comparable with the figure calculated by Hubble for
Birmingham in 1966 (1 in 7255) from case surveys.
Although Rudd's data concerned only one year,
they suggest that the rate of diagnosis by a non-
screening procedure in this region is consistent with
the expected incidence.

Our overall figures verify the finding of Lebovitz
et al that congenital adrenal hyperplasia frequently
remains undiagnosed in the neonatal period but
show that the diagnostic rate improved in the 1970s
compared with that of previous years in the West Midlands. The reasons for this improvement are
probably improved clinical awareness and better
diagnostic tests. The major advantage of neonatal
screening is the prevention of incorrect assignments
of sex and death due to adrenal crisis, and we are
not aware of the occurrence of either of these events
since 1970. The value of earlier diagnosis in those
infants who would be detected clinically, but later
than by a screening programme, is not known, and it
is therefore difficult to justify screening for this
reason alone. Neonatal screening is not without
problems; in particular, the interpretation of 17-OHP
concentrations in premature or sick newborn infants is
difficult. The anxiety generated by false positive
results needs to be balanced against the potential
advantages of a screening programme.

We are at present not convinced of the need for
a neonatal screening programme for congenital
adrenal hyperplasia in Birmingham or in the United
Kingdom as a whole.

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