Incidence of Salt-losing Form of Congenital Virilizing Adrenal Hyperplasia

The C-21 hydroxylase defect in the biosynthesis of adrenocortical steroids is the most common cause of congenital virilizing adrenal hyperplasia (CAH). Clinically and biochemically, two distinct forms of this syndrome are recognized: the non-salt-losing form and the salt-losing form. Since salt-losers and non-salt-losers generally occur in different families, it is believed that the two forms of CAH are genetically independent (Childs, Grumbach, and Van Wyk, 1956; Prader, Anders, and Habich, 1962).

Estimates for both forms of CAH in populations have ranged from 1 in 5,041 births in the canton of Zurich, Switzerland (Prader, 1958), to 1 in 67,000 births in Maryland (Childs et al., 1956). Assuming equal incidence for the two forms, Prader estimated the incidence of 1 in 12,500 births for the salt-losers and the non-salt-losers separately. The incidence of the salt-losing form alone has been reported to be 1 in 1,481 livebirths in Alaskan natives and 1 in 490 livebirths in Alaskan Yupik Eskimos (Hirschfeld and Fleishman, 1969). The present communication reports the incidence of the salt-losing form of CAH in Toronto, Canada.

**Summary**

Descriptions are given of two cases of gas in the portal venous system in association with duodenal obstruction and also one case with interstitial emphysema of the stomach.

I am grateful to Mr. D. G. Young and Mr. J. A. S. Dickson for their collaboration and for the co-operation of Messrs. Harvey Miller and Medcalf, Aylesbury.

**Patients and Methods**

Patients included in this report were born in metropolitan Toronto, a well-defined municipal area, between January 1960 and December 1967. The diagnosis of the salt-losing form of CAH was made on the basis of symptoms: typical of adrenal insufficiency (vomiting, diarrhea, failure to thrive, dehydration, electrolyte imbalance), ambiguous genitalia in female infants, and abnormal urinary steroid excretion.

Twelve patients (7 male and 5 female) with the salt-losing form of the syndrome were born during the 8-year period. These were all referred to The Hospital for Sick Children. Only one patient, a male, was diagnosed after necropsy. No additional cases were detected in other hospitals in the city. During the same period, there were 315,509 livebirths in the area.

**Results**

The incidence of the salt-losing form of CAH in Toronto was calculated to be 1 in 26,292 livebirths, with an estimated gene frequency of 0·00617 and heterozygote incidence of 1 in 82 livebirths (Table I). Since only proven cases were used, it is not possible that these figures could overestimate the true incidence in the period under consideration. The results of the present study are compared with those from other series in Table II.

**Discussion**

It is difficult to obtain complete ascertainment of patients with the non-salt-losing form of CAH in a population, since the diagnosis is either delayed, or not made at all. On the other hand, because of the life-threatening nature of the disease, patients with the salt-losing form of CAH usually present for treatment soon after birth (Iversen, 1955). Therefore, it is unlikely that any salt-losers born during the study period would be as yet undiscovered. Limiting the study to a definite geographical area
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**TABLE II**

**Incidence of CAH in Different Population Groups**

<table>
<thead>
<tr>
<th>Author</th>
<th>Population</th>
<th>Type of Disease</th>
<th>Patient/Livebirths</th>
<th>Heterozygotes/Livebirths†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Childs et al. (1956)</td>
<td>Maryland, U.S.A.</td>
<td>Both*</td>
<td>1 : 67,000</td>
<td>1 : 128</td>
</tr>
<tr>
<td>Prader (1958)</td>
<td>Canton of Zurich, Switzerland</td>
<td>Both*</td>
<td>1 : 5,041</td>
<td>1 : 35</td>
</tr>
<tr>
<td>Hubble (1966)</td>
<td>Birmingham, England</td>
<td>Both*</td>
<td>1 : 18,500</td>
<td>1 : 68</td>
</tr>
<tr>
<td>Hubble (1966)</td>
<td>Wisconsin, U.S.A.</td>
<td>Both*</td>
<td>1 : 15,000</td>
<td>—</td>
</tr>
<tr>
<td>Rosenbloom and Smith (1966)</td>
<td>Alaskan Natives</td>
<td>Salt-losing</td>
<td>1 : 1,481</td>
<td>1 : 20</td>
</tr>
<tr>
<td>Hirshfeld and Fleishman (1969)</td>
<td>Yupik Eskimos</td>
<td>Salt-losing</td>
<td>1 : 490</td>
<td>1 : 11</td>
</tr>
<tr>
<td>Present study</td>
<td>Toronto, Canada</td>
<td>Salt-losing</td>
<td>1 : 26,292</td>
<td>1 : 82</td>
</tr>
</tbody>
</table>

*Salt-losers and non-salt-losers.
†The figures in this column are those as given by the authors. Dr. Cedric O. Carter informs us that ‘the heterozygote frequency cannot be calculated by doubling the square root of the birth frequency where two different types, caused by two different genes, are involved’.  
—Editor

such as metropolitan Toronto, with adequate medical facilities, further assures complete ascertainment. In this context, it is of interest that Prader (1958) reported an incidence nearly 5 times higher of CAH for the canton of Zurich, than for the rest of Switzerland. This disparity was attributed by the author to failure to recognize many cases in the hinterlands.

Most published series (Childs et al., 1956; Prader, 1958; Hubble, 1966; Rosenbloom and Smith, 1966) have reported on the combined incidence of the two variants of CAH and cannot be compared with our data. The only figures available for comparison with our estimate of the incidence of the salt-losing form in Toronto (1 in 26,000 livebirths) are those obtained from the study of Alaskan natives and Yupik Eskimos (Hirshfeld and Fleishman, 1969). The unusually high incidence in the Alaskan natives (1/1,481) and in the Yupik Eskimos (1/490) has been attributed to the introduction of a deleterious allele into a genetic isolate without outbreeding.

If one assumes, as Prader (1958) did, equal incidence for both variants, the combined incidence for CAH in the present report would be 1 in 13,000 livebirths. This figure is comparable to that estimated by Rosenbloom and Smith (1966) (1/15,000). It is about 5 times that reported in Maryland (Childs et al., 1956) (1/67,000), and approximately one-half that reported in Birmingham, England (Hubble, 1966) (1/7,255) and in Zurich, Switzerland (Prader, 1958) (1/5,041). The very low incidence reported by Childs et al. in Maryland may be due to the fact that many cases might have remained unrecognized since two-thirds of the study period was before 1951, when diagnosis and therapy of CAH were difficult. The higher incidence in Birmingham and Zurich may represent more complete ascertainment in a more homogeneous population.

**Summary**

The incidence of the salt-losing form of congenital virilizing adrenal hyperplasia in Toronto has been derived from a count of all proven cases born in that city from January 1960 until December 1967. The incidence of the salt-losing form is estimated to be 1 in 26,000 births, with a gene frequency of 0.00617 and heterozygote incidence of 1 in 82 births. The only figures available for comparison with our estimate of the incidence of the salt-losing form in any population are those from the study of Alaskan natives and Yupik Eskimos who have an unusually high incidence of the condition.

**References**


Quinine Intoxication in a Child Treated by Exchange Transfusion

Quinine poisoning is rare in children. The mortality rate is high and in patients who survive serious intoxication there may be residual blindness and deafness. The following report shows that in childhood, exchange transfusion is an effective treatment.

**Case Report**

An 18-month-old Jamaican girl was brought to hospital 3 hours after being found at home eating her mother’s quinine sulphate tablets (300 mg). She was drowsy and twitching. A gastric washout retrieved a considerable quantity of tablet particles. The dose of quinine taken is unknown.

The child gradually became less responsive and the twitching became generalized. An intravenous infusion was begun in an attempt at forced diuresis. The fits were controlled by repeated doses of intravenous diazepam. A plasma level of quinine 4 hours after the ingestion of the tablets was 0·49 mg/100 ml. No other toxic substances were detected in blood or urine.

In spite of treatment the child’s condition continued to deteriorate. She became unrousable, her pupils became dilated and fixed, no reflexes could be obtained, and the fits were no longer controlled by diazepam. A lumbar puncture was performed, and this produced normal CSF.

In view of the clinical deterioration, it was decided to carry out an exchange blood transfusion, despite the apparently low levels of circulating quinine. In the course of 3 hours 1800 ml whole blood was exchanged using a central venous catheter. The plasma quinine levels estimated during the exchange transfusion are shown in the Fig. The quinine level in the CSF is also shown. The child stopped convulsing after 1000 ml blood had been exchanged and she became more responsive. Her blood pressure remained about 90/50 mm Hg throughout the exchange transfusion.

Twenty-four hours after admission the girl was alert, but unresponsive to sound and to light, her pupils remaining fixed and dilated. 5 days later, however, she had regained her hearing, and her visual acuity on formal testing was estimated as 6/12.

**Comment**

The signs and symptoms of quinine overdose are well described (Goodman and Gilman, 1970). Tinnitus, tremor, vomiting, and hypotension occur early, rapidly followed by convulsions and loss of consciousness. Some individuals display an idiosyncratic hypersensitivity to quinine, and may show toxic manifestations at therapeutic plasma levels. In the present case, despite recovering tablet particles by gastric lavage, the child lapsed into unconsciousness and began to convulse within 3 hours of ingesting quinine. This presumably reflects the fact that quinine is rapidly absorbed from the stomach and small intestine, maximum plasma levels being reached within 4 hours.

Quinine in therapeutic doses is rapidly metabolized and is excreted in the urine within 24 hours (Goodman and Gilman, 1970). The slow fall in the level of blood quinine in this child, before exchange transfusion, suggests that its clearance may be impaired at toxic levels, or that she continued to absorb quinine from the intestine. Some 70% of quinine in the plasma is bound to plasma proteins (Goodman and Gilman, 1970).

Therapeutic levels of plasma quinine in adults are in the region of 0·7 mg/100 ml. In the present case, the maximum level of plasma quinine recorded (0·49 mg/100 ml) was considerably less than the levels of 26–33 mg/l. quoted by Hillman and Harpur (1961) in their report of exchange transfusion in the treatment of quinine poisoning.
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