THE PROGNOSIS OF IDIOPATHIC RENAL ACIDOSIS IN INFANCY WITH OBSERVATIONS ON URINE ACIDIFICATION AND AMMONIA PRODUCTION IN CHILDREN

BY

ELIZABETH U. BUCHANAN and G. M. KOMROWER

From the Royal Manchester Children's Hospital and the Department of Paediatrics and Child Health, University of Manchester

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Idiopathic renal acidosis of infancy has been recognized for over 20 years since the descriptions of the morbid anatomy by Lightwood (1935) and of the clinical condition by Butler, Wilson and Farber (1936). The incidence of the condition appeared to reach a peak between 1946 and 1952 during which time 35 cases were described in The Hospital for Sick Children, London (Lightwood, Payne and Black, 1953), while 17 cases were seen in the Birmingham Children’s Hospital between 1948 and 1953 (Carré, Wood and Smallwood, 1954). The prognosis has been stated to be good in infants surviving the acute phase of the illness (Hartmann, 1939; Stapleton, 1949; Lightwood et al., 1953) but only isolated cases have been followed for any number of years after recovery (Kelsey, Reinhart and Fishel, 1950; Doxiadis, 1952). Our colleagues, seeing cases of renal tubular acidosis in adults, have been interested to know whether there is any relationship between this condition and that seen in infancy. It was, therefore, felt worth while to make a detailed survey of the eight children who had been in the Royal Manchester Children’s Hospital with infantile renal acidosis between 1948 and 1953 and who, by the time of the review, were between 5 and 10 years of age and had been off all treatment for periods ranging from three and a half to nine years.

The review which was carried out in 1957 included recent history, physical examination, a radiograph of the abdomen to detect renal calcification, and examination of blood and urine. Distal renal tubular function was examined by a test designed to assess powers of concentration and dilution at the same time as the ability to secrete an acid urine and to form ammonia following the administration of ammonium chloride. We could find no data on normal values in children for urine acidification and ammonia production following oral ammonium chloride, so it was necessary to carry out observations on a control series.

Methods

Twenty-two normal children formed the control series. In selecting cases for this series the following criteria were observed: the child was considered to have recovered from the condition for which he had been admitted to hospital and was about to be discharged (the majority being surgical cases on the day before discharge); secondly, there was no history of renal disease, no abnormality was detected in the urine and the concentration and dilution test was normal.

The technique used for the combined concentration and dilution and acidification test was as follows. Fluids were restricted from 8.30 p.m. on the evening preceding the test until 12.30 p.m. next day, but solid foods were allowed. The child emptied his bladder at 8.30 p.m., 12.30 a.m. and 6.30 a.m.; the specific gravity was measured and the urine discarded. At 8.30 a.m. and 9.30 a.m. the child again emptied his bladder; the volume and specific gravity of the urine were measured and a specimen preserved with thymol for estimation of pH and ammonium content. Between 9.30 a.m. and 10.30 a.m. the child was given ammonium chloride in a dose of 0.1 g. per Kg. body weight (the salt being given in gelatine capsules in every instance except one where difficulty was encountered with swallowing, and a mixture was given instead). During that hour the child was also given 20 ml. water per Kg. body weight. The ammonium chloride was given over an hour to avoid nausea, and difficulty in this respect arose in only one instance. The child having the test emptied his bladder at 11.30 a.m. and this specimen was discarded. This procedure was followed to eliminate the fluctuations in ammonia production during this period resulting from the variable initial urine pH. In this way it was possible to assess more accurately the effect of the ammonium chloride. The bladder was emptied at 12.30 p.m., 2.30 p.m. and 4.30 p.m.; urine passed between these times...
was mixed with the next timed specimen; all collections of urine were preserved with thymol. The volume and specific gravity of each specimen was measured and pH and ammonium content estimated. The pH was measured by means of the B.D.H. capillator. Ammonium was estimated using Conway's microdiffusion units, the rate of excretion in micro-equivalents per minute being calculated in each period and also over the two to seven-hour period following the administration of the drug.

In every case the urine pH fell below 5.3 within five hours of the administration of ammonium chloride, the range being from 4.8 to 5.2 on the B.D.H. capillator. The values obtained by this means are only accurate to within 0.2 in either direction. This has been determined by comparison with values obtained on a glass electrode pH meter. It has been found, however, that when the pH is below 5.7 the figures obtained with the B.D.H. capillator is consistently higher than that obtained with the glass electrode pH meter. It seems likely, therefore, that the ability of these children to acidify urine is even greater than that shown by our results.

The rate of ammonium excretion in the five-hour period under investigation varied considerably from one child to another but was found to bear a close relationship to the child's weight. The results obtained in the 22 normal children are shown on the accompanying graph which also includes figures for normal adult controls obtained during a similar investigation in adults. In this investigation ammonium excretion was estimated over the two to eight-hour period after ammonium chloride (Wrong and Davies, 1959, in press).

Cases Under Review

The eight children who had been in the Royal Manchester Children's Hospital with infantile renal acidosis between 1948 and 1953 had all been under the care of one of us (G.M.K.): five were boys and three girls. All had been admitted to hospital between the ages of 5 and 11 months, their symptoms having begun at between 3½ and 8 months of age. With one exception they had presented three or more of the recognized features of constipation, vomiting, anorexia, failure to gain weight and polyuria. In the exception the only presenting feature was failure to gain weight. Physical examination on admission had shown two or more of the recognized signs of hypotonia, wasting, dehydration, malar flush and palpable faeces in the abdomen. In every case except one (R.M., see Appendix) the diagnosis was confirmed shortly after admission by the finding of a systemic acidosis with serum bicarbonate of less than 35 vol. % (16 mEq./l.) associated with alkaline or faintly acid urine, the pH ranging from 6.9 to 7.9. The serum chloride was raised above 640 mg. % as sodium chloride (110 mEq./l.) in the five cases in which the estimation was carried out before treatment was begun. With one exception (R.M.) the blood urea did not rise above 50 mg. % and returned rapidly to normal when treatment was begun. Radiographs of the abdomen showed no evidence of renal calcification in any patient. In seven cases (excluding R.M.) treatment with alkalis was given, sodium citrate and citric acid being used initially and potassium citrate added later if necessary. Hartmann's solution and M/6 lactate were used in the early stages of treatment especially in the four cases where parenteral fluids were required. Treatment was continued until the biochemistry remained normal after a trial period without alkali. The length of treatment varied from five to 23 months. All the children except one were able to stop treatment between the age of 15 and 21 months. The one exception was an infant who had been very difficult to control when treatment was initiated. In her case treatment had to be continued until she was 2 years 4 months old.

All the children attended the out-patient department at intervals until 1954 and their progress was considered to be satisfactory.

The review carried out in 1957 comprised two stages. In the first the children were seen as out-patients and the object of the review explained to the parents. The recent history was obtained, a physical examination carried out and a radiograph of the abdomen taken. In the second stage the child was admitted to hospital for 36 hours for examination of blood and urine, followed by the combined concentration, dilution and acidification test already described.

In every case the parents were well pleased with the child's progress and no abnormality was found on physical examination which included blood pressure estimation. Heights were close to the 50 percentile for the corresponding age, but weights were rather below it with two girls close to the 10 percentile. The percentiles used were those calculated by Tanner (1958) from data provided by Scott (1955). It is interesting, though probably not significant, that the two underweight girls were the patients whom it had been most difficult to control at the onset of treatment. A radiograph of the abdomen revealed no evidence of renal calcification in any of the children. Urine examination, including microscopy, showed no abnormality. Blood chemistry comprised serum calcium, phosphorus, chloride and bicarbonate and blood urea. The values obtained were normal in every case with the exception of the blood urea in R.M. (see Appendix).

The test designed to assess distal renal tubular function showed very satisfactory results. After 13 hours' deprivation of fluid the urine specific gravity rose to between 1,018 and 1,025, while after
taking water (20 ml per kg.) it fell to 1,001 or 1,000. Following ammonium chloride the urine pH fell to between 5·0 and 5·2 in every case and, bearing in mind the remarks made in connexion with the control series, the actual acidity of the urine may well have been greater. Ammonium excretion is plotted against weight in Fig. 1 and shows that these children fall within the range determined for the control series.

Conclusion

The results of the investigation confirm the clinical impression that idiopathic renal acidosis of infancy is a self-limiting disease if the affected children are brought safely through the acute phase. In particular it shows complete recovery of the ability to secrete an acid urine (Fig. 2) and to form ammonia (the latter ability being present but impaired during the acute illness) (Latner and Burnard, 1950). From these results it appears that renal acidosis associated with nephrocalcinosis in older children and adults is a different condition from infantile renal acidosis and that the one does not lead to the other.

This work was done while one of us (E.U.B.) was holding the Ashby Memorial Research Scholarship of the University of Manchester.

We should like to thank Dr. O. Wrong for permission to include his figures for adults in the graph and for his co-operation, and Miss V. K. Wilson for advice and assistance on biochemistry.

APPENDIX

Case History

R.M., a first-born male child, was born on September 15, 1947, and was admitted to the Royal Manchester Children's Hospital at the age of 7 months on account of a two-month history of anorexia, loss of weight, fretfulness, constipation and intermittent vomiting. The pregnancy and delivery had been uneventful, and birth weight was 8§ lb. He had been breast fed for only 2 weeks, and was then changed to National Dried Milk on which he continued to thrive until he was 5 months of age. Thereafter he lost 1 lb. 10 oz. in weight in five weeks. When seen at 7 months he weighed only 14 lb. 6 oz. Apart from obvious loss of weight and dehydration, the only abnormal feature was a flush over the malar bones unassociated with pyrexia. Following admission he developed an irregular pyrexia and his weight remained stationary. Investigations included a Mantoux test, 1 in 1,000, which was negative, radiographs of chest and wrist which were both normal, haemoglobin 78% (11·5 g. %) with colour index 0·93, white cell count 12,000 with normal differen-

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tial. Throughout his stay in hospital there was constant slight albuminuria and the urine specific gravity never rose above 1,010. He had intermittent pyrexia, and urine culture twice yielded *Strep.* faecalis which cleared following courses of sulphadimidine and penicillin. The urine was usually neutral or alkaline but on one occasion was acid to litmus. Blood urea was 57 mg. % on admission and rose to 105 mg. %. Intravenous pyelogram showed poor excretion of dye but no obvious renal abnormality. In the last week in hospital his weight gain improved and when discharged on June 17, 1948, he weighed 15 lb. 4 oz. From July 6 to July 28, 1948, he was an in-patient at Birmingham Children's Hospital. There he was found to have hyperchloraemia (698 mg. % as sodium chloride), a low alkali reserve (25·5 vol. %) and a serum calcium of 11·2 mg. % and a diagnosis of infantile renal acidosis was made. The urine still contained a trace of albumin and some pus cells, and the ammonia content of a 24-hour specimen was only 0·11 g. By this time there was a marked improvement in his clinical condition and his blood urea had fallen to 50 mg. %. Treatment with alkalis was therefore not considered necessary. He took his feeds well and gained weight steadily and when discharged at the age of 10½ months he weighed 17 lb.

R.M. was seen as an out-patient in Manchester at regular intervals during the next 5½ years. His progress was rather slow until he reached 2 years of age but thereafter his height and weight were well up to the average for his age and no abnormality was found on physical examination, which included blood pressure estimation. His blood urea, however, remained above normal except on one occasion in 1954 when it was 29 mg. %. When reviewed in 1957 at the age of 9 years, 10 months, his height and weight were close to the 90 percentile for his age and he appeared to be very well. Blood pressure was 95/60 and a radiograph of the abdomen revealed no renal calcification. Urine examination, including microscopy, showed no abnormality and the concentration and dilution test gave a specific gravity range of 1,022 to 1,002 after 13 hours' deprivation of fluid. In the acidification test his performance was well up to the average, the urine pH falling to 5·2 after three hours and the rate of ammonium excretion being well within the normal range for that weight (see Fig. 1). Serum electrolytes were within normal limits but blood urea was still 43 mg. %; six months later this had fallen to 38 mg. % while the urea clearance was 72 % of average normal function. In this boy, therefore, renal tubular function now appears to be restored to normal but there is still some doubt about glomerular function. The height to which the blood urea rose in the acute phase of the illness suggests that there may have been some glomerular damage at that time, and that this illness may not have been a pure idiopathic renal acidosis of infancy.
The Prognosis of Idiopathic Renal Acidosis in Infancy with Observations on Urine Acidification and Ammonia Production in Children

Elizabeth U. Buchanan and G. M. Komrower

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