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LACTOSURIA AND AMINO-ACIDURIA IN INFANCY

A CASE REPORT

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Several reports describing carbohydrate intolerance in infancy as a result of intestinal carbohydrase deficiencies have recently appeared. Darling *et al.*[1] reported the finding of considerable lactosuria and amino-aciduria in two related infants who presented with failure to thrive, diarrhoea and vomiting. The condition proved fatal in both cases. Holzel *et al.*[2] described a similar clinical presentation in two siblings. Diarrhoea and failure to thrive while on milk were the main signs. On a lactose-free diet both infants improved and progress was maintained. Lactose-tolerance tests confirmed the inability to metabolize this sugar. No reference was made to amino-aciduria or lactosuria. Further, Weijers *et al.*,[3] in a preliminary communication, reported the investigation of patients suffering from invertase and/or maltase deficiencies. They had also seen cases of lactase deficiency. Again, no reference was made to amino-aciduria or the finding of sugars in the urine. Inall[4] reported that both sucrose and lactose appeared in the urine while the patient was receiving these sugars. Improvement followed the introduction of lactose- and sucrose-free diets accompanied by the disappearance of these sugars from the urine. No amino-aciduria was present.

The basic biochemical lesion in all these cases appeared to be an absence or deficiency of the particular carbohydrate-splitting enzyme in the intestine. The ingested disaccharide could therefore not be split into its monosaccharide components. This resulted in abnormal fermentation in the bowel from bacterial action on the sugars with the production of large quantities of lactic acid and other volatile fatty acids.[3] These substances produce bowel irritation, increased peristalsis and diarrhoea. Some of the unsplit sugar may be absorbed, but because it cannot be utilized it is rapidly excreted in the urine.

A patient resembling those described by Darling *et al.*,[1] with lactosuria and amino-aciduria, was admitted to Groote Schuur Hospital, Cape Town, recently. The lactosuria was, however, not recognized initially, through failure to examine the urine by a reduction method in addition to methods specific for glucose ('tes-tape').

CASE REPORT

A European girl, aged 2 months, was admitted to the paediatric ward under the care of one of us (H. de V. H.). The infant was delivered at home, weighing 5 lb. 8 oz., after a gestation period of 37 weeks. The immediate neonatal period was apparently uneventful except for failure to gain weight normally. Breast feeding was stopped after 2 weeks and was followed by artificial feeding with full-cream milk. Loose green stools and vomiting began at the age of 1 month. No relevant family history was obtained from the father, aged 27 years, and the mother, aged 24 years. Two siblings, a boy aged 3 years and a girl aged 2 years, were healthy.

On admission, the infant weighed 6 lb. 6 oz. and was moderately dehydrated, with pallor of the mucous membranes and a scaly rash on the trunk. Clinical examination showed no other abnormalities and no changes were noted in the corneas, lenses, anterior or posterior chambers, and retinae of the eyes.

Blood haemoglobin concentration was 9·5G. per 100 ml. and white blood count 22,000 per c.mm. Urine was acid to litmus paper, contained a trace of protein but no glucose (tes-tape), ketones, bilirubin or urobilin, and there was an essentially normal spun deposit.

After a provisional diagnosis of gastro-enteritis had been made, therapy with intravenous half-strength Darrow's solution, containing 2·5% dextrose, was begun. In addition, the infant received antibiotics. Intravenous therapy was discontinued after 24 hours and was followed by half-strength Darrow's solution, 5% dextrose and, subsequently, oral skimmed milk. After 4 days on this régime, clinical improvement was evident, accompanied by a gain in weight of 11 oz. The feed was now changed to half-cream milk. Shortly afterwards diarrhoea re-appeared with rapid clinical deterioration and dehydration. The infant remained apyrexial and repeated stool cultures, blood culture and cerebrospinal-fluid examination yielded negative results.

Some improvement followed further intravenous therapy. On the tenth day after admission, a reducing substance yielding a brick-red deposit on testing by Benedict's qualitative method was detected in the urine. This was confirmed on subsequent testing. The urine had been tested several times previously but only with tes-tape (glucose-oxidase). Blood-sugar levels at the time of the Benedict tests were 43 and 62 mg. per 100 ml. (Hagedorn and Jensen).

Further episodes of diarrhoea and rapid dehydration warranted the administration of hydrocortisone intravenously. Acidosis (serum bicarbonate of 12·5 mEq. per litre) was treated satisfactorily with a solution containing 30% potassium citrate and 30% sodium citrate. A blood transfusion corrected the anaemia. Further fluid requirements were guided by frequent serum-electrolyte determinations. However, in spite of temporary remissions while on intravenous therapy, relapses regularly recurred on oral feeding with milk, since the significance of the positive Benedict's test was not appreciated early, and the infant died 25 days after admission, before a definite diagnosis could be made.

Results of additional special investigations were: serum albumin 2·1G. per 100 ml., globulin 1·4G. per 100 ml., serum cholesterol 47 mg. per 100 ml., inorganic phosphorus 3·4 mg. per 100 ml., alkaline phosphatase 5 units per ml. (Bodansky). X-ray examination of chest, wrists and abdomen was normal. Wassermann and Berger reactions were negative.

Special Methods

A 24-hour specimen of urine was submitted late in the illness for identification of the reducing substance in the urine and for testing the presence of amino-aciduria.

The reducing substance was identified by one-dimensional chromatography, using a solution containing xylose, fructose, glucose, sucrose, lactose and galactose as reference markers. In 2 different solvent systems—isopropanol-water, 160:40, and n-propanol-ethyl acetate-water, 140:20:40—the R_F* of the unknown corresponded exactly to that of lactose. The aniline diphenylamine reagent was used for locating the sugars.

For amino-acid chromatography an aliquot of the urine was

* R_F (ratio of flow) represents the distance the material has moved from the original point of application divided by the distance the solvent front has travelled from that point.

desalted in an ion-exchange column containing zeocarb 225 in the hydrogen cycle followed by elution with concentrated ammonia.[5]

Two-dimensional paper chromatography was performed on Whatman's No. 1 paper using as first solvent butanol-acetic acid-water, 120:30:50, followed by t-butanol-methyl ethyl ketone-ammonia (S.G. 0·880)-water, 40:40:10:20. Ninhydrin, 0·2% in acetone, was used as location reagent. This showed a generalized amino-aciduria (Fig. 1).

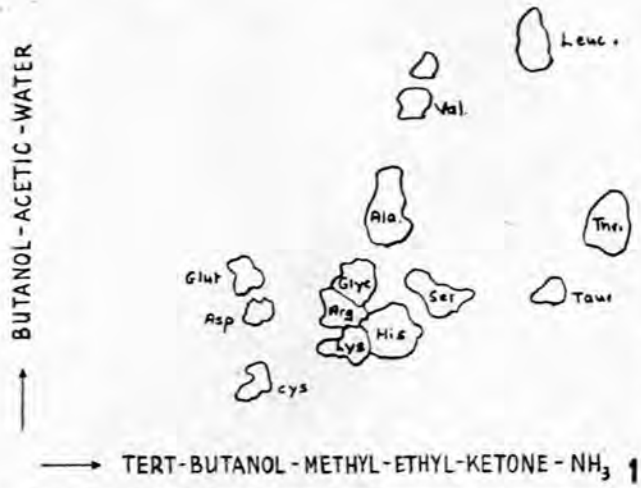

Fig. 1: Tracing of original amino-acid chromatogram. Glut. = glutamic acid, Asp. = aspartic acid, Cys. = cystine, Lys. = lysine, Arg. = arginine, Glyc. = glycine, Ala. = alanine, Ser. = serine, Taur. = taurine, Thr. = threonine, Leuc. = leucine, Val. = valine, and His. = histidine.

Summary of Autopsy Findings

The body was that of an oedematous female infant weighing 2,740 grams. Apart from focal areas of collapse in both lungs and a moderate degree of fatty change in the liver, the only significant abnormalities were confined to the rectum. Four small ulcers, 1 - 2 mm. in diameter, were present in the lower rectum. The intervening mucosa was normal. The stomach, duodenum and proximal jejunum were free of lesions. The rest of the bowel was accidentally discarded before it could be examined in detail, but on preliminary inspection no obvious abnormalities were noted.

Histologically the lesions in the rectum appeared to be acute submucosal abscesses. Definite ulceration could not be demonstrated in the sections examined. The exact nature of these lesions could not be determined and postmortem bacteriological examination failed to reveal any pathogens.

DISCUSSION

Although the delay in detecting the reducing substance in the urine of this infant prevented complete biochemical investigation, the clinical presentation associated with amino-aciduria and lactosuria suggests that she suffered from a condition similar to that described by Darling *et al.*[1] The rapid deterioration each time a change was made to a milk-containing feed, with remissions while on intravenous therapy, lends further support.

Small quantities of lactose are commonly found in the urine of newborn and especially premature infants. The amount excreted is usually less than 100 mg. per 100 ml. and is often detected by chromatographic methods only.[6] This is thought to be due to inadequate lactase activity, because this enzyme is the last of the disaccharidases to appear and may not be present until the eighth foetal month.[7] For this reason the mere finding of traces of lactose in the urine of newborn children is not sufficient evidence for diagnosing this syndrome. Similarly, amino-aciduria may occur in the premature and newborn infant. Although quantitative urinary lactose estimation was not performed in this case, the brick-red deposit constantly obtained on qualitative testing with Benedict's reagent indicated a urinary concentration of at least 2 G. per 100 ml. This finding in the presence of blood-sugar levels of only 43 and 62 mg. per 100 ml. does indicate significant lactose intolerance.

Neither Holzel *et al.*[2] nor Weijers *et al.*[3] referred to urinary findings in their cases. The incidence of amino-aciduria and the frequency with which the offending sugar occurs in the urine can therefore not be assessed.

A hereditary basis seems likely since the condition has been found in siblings.[1,2] The father, mother and siblings of the present patient were investigated for lactosuria with negative results. It has not yet been established whether the condition is a permanent defect or just delayed maturation of the enzyme system. Holzel *et al.*[2] stated that their patients were perfectly well at the ages of 15 months and 10 years respectively, but made no reference to lactose tolerances at those ages. This may therefore be a temporary inability to metabolize these disaccharides efficiently, and speculations as to possible relationships between carbohydrate and amino-acid anomalies would appear untimely at this stage.

The importance of recognizing the condition and removing the offending sugar from the diet is obvious, because in addition to producing diarrhoea, hypoglycaemia may be a serious complication due to inability to metabolize the available carbohydrate.

Weijers *et al.*[3] found significantly raised levels of lactic acid and volatile fatty acids in the stools of their patients. If the faecal lactic excretion exceeds 1 gram in 48 hours, carbohydrate intolerance should be considered as a probable cause. Suitable carbohydrate-tolerance tests employing the various disaccharides will confirm the diagnosis and determine which enzyme is deficient.

The danger of omitting to test urine by a reduction method in addition to methods specific for glucose (glucose-oxidase) is well illustrated by this case, since an important diagnostic clue was overlooked at first.

SUMMARY

A fatal case of amino-aciduria and lactosuria is described and the findings in other reported cases presenting with similar syndromes are briefly reviewed.

The importance of employing a reduction test, in addition to a glucose-specific method, as a screening test for the presence of urinary sugar in early infancy is stressed, particularly in view of the possibility of successful therapy being instituted on detecting such an abnormality.

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