Case report

Chronic vomiting in a case of citrullinaemia detected after treatment by total parenteral nutrition

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SUMMARY We report a case of a 56 year old woman who presented with a long history of chronic attacks of vomiting. On admission to hospital she was cachectic, and attempted parenteral nutrition induced coma. The illness was found to be due to citrullinaemia, a metabolic disorder of the urea cycle. Our patient is the oldest with this disorder so far described in the literature. The main points of the case and its investigation are outlined: hyperammonaemia, amino acid chromatogram, measurement of enzyme activity in skin and liver biopsy material. The therapeutic measures which led to cure are of particular interest.

Chronic vomiting in an adult patient without evidence of organic lesions of the gastrointestinal tract or the central nervous system is often considered to be psychogenic.¹ In children, chronic vomiting is a well known symptom of a metabolic disorder, especially one of urea synthesis leading to hyperammonaemia. Citrullinaemia, a result of an hereditary deficiency of argininosuccinate synthetase, is one of these metabolic diseases. Many cases have been reported in neonates and children, but adult cases are very rare in white people.^{2,3} We report here the case of an adult female (aged 56 years) with a long history of chronic vomiting traced to citrullinaemia with concomitant bouts of hyperammonaemia. This is the oldest patient so far described.

Case report

A 56 year old white woman was referred to our department in October 1980 with cachexia and a long history of chronic cyclic vomiting which had begun in her infancy. There was no past record of such vomiting in her parents and relatives, but her two brothers died shortly after birth of an undetermined cause. The patient's pregnancy and delivery

were normal. She complained of recurring prolonged attacks of severe vomiting without any evident cause since the age of seven. Attacks of vomiting began suddenly, lasted several days and stopped spontaneously. From 1973 until 1980 she lost weight. Laboratory tests, radiological and endoscopic studies did not lead to any definite diagnosis. In April 1980 vomiting became persistent, so that her overall weight loss was estimated to be 20 kg. She was then referred to a surgical unit where a vagotomy and antrectomy were performed in spite of a normal upper gastrointestinal endoscopy. A liver biopsy taken at operation revealed steatosis. After the operation she was placed under total parenteral nutrition. Within three days she went into an unresponsive coma.

The features of the EEG were those of a diffuse degenerative disease with metabolically suppressed electrical activity and multiple seizure foci. The cranoscan was normal. Total parenteral nutrition was then discontinued and the patient recovered completely from coma, but vomiting still continued. In the absence of a diagnosis she was allowed to return home. As vomiting persisted she was finally referred to our department in October 1980. Her weight was then 36 kg for a height of 158 cm. The clinical examination was normal except for evidence of malnutrition and dehydration. Laboratory tests showed: Hb 8.65/ml, protein 50 g/l, albumin 27 g/l. Other tests, especially liver function tests, were

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normal. Complete radiological and endoscopic examinations of the gastrointestinal tract detected no abnormality. Total parenteral nutrition was started, leading within two days to another episode of coma which resolved as soon as the total parenteral nutrition was stopped. A metabolic disorder was suspected, and further confirmed by the association of a raised serum ammonia and a characteristic pattern on the serum amino acid chromatogram (Table 1). The striking abnormality on the chromatogram was hypercitrullinaemia, but both ornithine and methionine were outside the normal range. These features were confirmed by another chromatogram and measurement of serum ammonia (Table 1). Unfortunately, it was not possible to obtain a new liver biopsy from the patient, but fibroblasts from a skin biopsy were grown in culture. Argininosuccinate synthetase activity was measured using the incorporation of radioactivity from $1\text{-}^{14}\text{C}$ -citrulline into cell proteins, as described previously.⁴

Results are shown in Table 2. Our case exhibited an argininosuccinate synthetase activity close to the results obtained from the heterozygous parents of a citrullinaemic child with total argininosuccinate synthetase deficiency.⁵ A special low protein diet (40 g/day) supplemented with arginine (3 g/day) was prescribed. The patient stopped vomiting com-

Table 2 Arginino succinate synthetase activity in fibroblast. The cells are incubated during 6 h or 24 h with $0.25\text{ }\mu\text{Ci}$ of $1\text{-}^{14}\text{C}$ -citrulline and $2\text{ }\mu\text{Ci}$ of $2\text{-}^3\text{H}$ -L-phenylalanine as previously described²

	Incubation time	
	6 hours	24 hours
Control skin fibroblast (17)	27.79 $\pm$ 4.65	45.11 $\pm$ 7.34
Prenatal citrullinaemic skin fibroblast (14)	0.70 $\pm$ 0.28	0.32 $\pm$ 0.12
Heterozygotes		
(Parents of citrullinaemic patients)		
SM	14.76	27.83
SS	15.67	35.46
JC	11.68	27.63
JM	8.25	25.04
Mad C 1 Assay	18.60	28.3
2 Assay	12.80	

Results are expressed as the ratio $^{14}\text{C}/^3\text{H}$ cpm $\times$ 100 into protein (mean $\pm$ SEM).

pletely, her condition gradually improved and she gained weight (8 kg over one year). Serum citrulline and ammonia concentrations decreased at the same time.

Discussion

Citrullinaemia is an inherited metabolic disorder affecting an enzyme in the urea cycle, argininosuccinate synthetase.⁶ This enzyme which is present in liver, kidney, brain, and fibroblasts³ transforms citrulline to argininosuccinic acid. When argininosuccinate synthetase activity is reduced, its normal substrates accumulate – namely, citrulline and ammonia. Higher concentrations of these two compounds are responsible for most of the pathological consequences of this enzyme defect.^{2,7,8} The first cases were published by MacMurray^{6,9} in 1962 and Morrow in 1967.¹⁰ Since then about 20 cases have been reported.^{2,7} The diagnosis is generally made in the neonate, rarely in adults. The oldest cases so far reported were 33 and 48 years old at the time of the diagnosis.^{11,12} Our case is thus the oldest so far described.

The clinical symptoms frequently described⁷ are of chronic anorexia and vomiting usually starting in infancy. Neurological disorders are common, consisting of irritability, episodes of confusion, and sometimes coma. The disease follows a cyclic course and mental retardation is common. On clinical examination an enlarged liver is sometimes found. Haemorrhage caused by deficiency in liver coagulation factors may occur.⁸ Biochemically, hypoproteinaemia related to undernutrition, raised serum concentrations of transaminases, and

Table 1 Variation of amino acids levels and ammoniaemia to nutrients

Amino acids	Normal ($\mu\text{mol/l}$ values litres)	Light protein diet PTN	Normal diet	Low protein diet
Taurine				71-615
OH proline	Trace	18-145	27-735	13-684
Threonine	138 $\pm$ 31	184-290	161-140	208-080
Serine	99 $\pm$ 19	72-107	55-611	49-418
Glutamic acid	34 $\pm$ 12	112-790	46-952	73-835
Proline	145 $\pm$ 48	200-000	207-562	226-292
Glycine	284 $\pm$ 44	176-020	157-230	138-830
Alanine	360 $\pm$ 71	176-730	229-710	245-700
Citrulline	Trace	766-180	105-010	99-100
Valine	225 $\pm$ 40	93-972	98-249	153-100
Cystine	49 $\pm$ 0.9	131-550	152-670	135-770
Methionine	21 $\pm$ 0.4	582-300	30-818	36-997
Isoleucine	60 $\pm$ 12	29-515	34-527	55-806
Leucine	115 $\pm$ 23	49-085	52-392	85-459
Tyrosine	54 $\pm$ 11	62-999	37-367	46-127
Phenylalanine	48 $\pm$ 0.7	65-167	42-292	50-178
Ornithine	58 $\pm$ 14	372-050	112-460	164-320
Lysine	186 $\pm$ 36	170-290	152-600	127-840
Histidine	88 $\pm$ 16	60-301	68-579	86-129
Arginine	82 $\pm$ 17	125-26	74-965	59-854
Aspartic acid	Trace	6-079	2-730	5-117
Ammoniaemia (mEq/l)		160	135	

coagulation disorders are found in acute stages of the disease.³

Our patient had a long history of vomiting, and coma was always induced by a high protein diet during total parenteral nutrition. When suspected, the diagnosis can be confirmed by three kinds of laboratory test:

(1) Hyperammonaemia is common and can be induced by a high protein diet.⁶ This is somewhat non-specific. (2) The amino acid chromatogram shows an extremely high concentration of citrulline in both blood and urine, sometimes associated with raised levels of alanine, lysine, glutamine, and methionine.¹¹ Ammonia and citrulline concentrations are also raised in cerebrospinal fluid.³ (3) Low argininosuccinate synthetase activity in hepatocytes or in fibroblasts can be assayed in liver biopsy specimens and skin fibroblast cultures. Our patient was mildly deficient in argininosuccinate synthetase activity, she must have been a heterozygote, as in a previously reported family⁵ relatives exhibited plasma citrulline levels 1.5 to five times the normal values. This is close to that found for our patient when she was on a normal diet. Heterozygous parents or relatives with clinical symptoms as severe as those observed in our case, however, have never been described. A partial homozygote with kinetic abnormalities could be hypothesised in our case. Although the argininosuccinate synthetase activity in fibroblasts was not greatly reduced, it may be that the liver enzyme was less active. Difference in activity between the two enzymes have been reported recently.¹³

Therapeutic measures consisted mainly of a low protein diet (2 g/kg/day) supplemented with arginine (3 g/day).¹⁴ This is one of the most effective ways of reducing citrulline levels. Some authors have suggested treatment with ketoanalogues^{5,14} and recent studies confirmed that administration of citrate¹² or sodium benzoate¹⁶ are effective in reducing the rise in blood ammonia.

After treatment our patient's health greatly improved and she gained 6 kg within the next four months. She had no further attacks of vomiting.

In conclusion, citrullinaemia is a rare cause of chronic vomiting which must be suspected even in adults when no other organic cause has been found, and especially when it is related to a high protein

intake. Therapeutic measures are simple and can enormously improve the patient's condition.

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