A Defect in Branched-Chain Amino Acid Metabolism in a Patient with Congenital Lactic Acidosis due to Dihydrolipoyl Dehydrogenase Deficiency

JENNIFER TAYLOR, BRIAN H. ROBINSON,[15] AND W. GEOFFREY SHERWOOD

Departments of Paediatrics and Biochemistry, University of Toronto; and Research Institute, The Hospital for Sick Children, Toronto, Ontario, Canada

Summary

In a case of dihydrolipoyl dehydrogenase deficiency, there was not only an elevation of lactate and α-ketoglutarate but also of branched chain amino acids. The levels of branched-chain amino acids varied from the normal range to three times the upper limit of normal during the patient's lifetime, and allo-isoleucine was detectable at all times. Examination of postmortem tissues revealed that the activity of branched-chain keto acid dehydrogenases was between zero and 10% of that in control tissues. It is suggested that the multiple defects seen in oxidative decarboxylation in this patient is the consequence of a single genetic deletion of an enzyme common to pyruvate dehydrogenase, α-ketoglutarate dehydrogenase, and branched-chain keto acid dehydrogenases.

Speculation

The dihydrolipoyl dehydrogenase component of pyruvate, α-ketoglutarate, and branched-chain keto acid dehydrogenases is genetically and biochemically a single entity.

We recently reported a case of congenital lactic acidosis which was found to be due to a deficiency of the third component of the pyruvate dehydrogenase complex (E_3). This deficiency was found to compromise the activity also of the α-ketoglutarate dehydrogenase complex; indicating that dihydrolipoyl dehydrogenase is shared in common by these two enzymes (8). The patient concerned had elevated levels of branched-chain amino acids indicating a possible involvement of the branched-chain keto acid dehydrogenases in the pathogenesis of this disease. In this brief communication we demonstrate in post mortem tissue from this patient that the branched-chain keto acid dehydrogenase activity is deficient and that the defect is not associated with the decarboxylase portion of the enzyme complex.

CASE REPORT

Details of the case report are described in reference (8). Levels of branched chain amino acids throughout the life of the patient are shown in Figure 1.

MATERIALS AND METHODS

Branched-chain keto acid dehydrogenase was measured by the modified method of Taylor et al. (11), using {1-^{14}C}-branched-chain keto acids prepared from the corresponding 1-^{14}C-amino acids by the method of Rudiger et al. (9). Branched-chain keto acid decarboxylase was measured by the modified method of Reed and Willms (7).

RESULTS

PLASMA AMINO ACID LEVELS

The levels of all three branched-chain amino acids were measured several times during the patient's five months in hospital . They appeared to be uniformely elevated on five out of the eight times that they were measured (Fig. 1); on two occasions to markedly high levels. Levels of alloisoleucine of 10, 14 and 14μM were detected on three occasions, there being a trace at the other times of measurement. Alloisoleucine is undetectable in the plasma of the normal individual.

POST MORTEM STUDIES

Total α-ketoisocaproate dehydrogenase measured on post mortem kidney, liver, and brain showed that the patient had less than 10% of normal activity in each case compared to the other controls, Table 1. α-Ketoisocaproate decarboxylase, on the other hand, appeared to be in the normal range in both brain and kidney, but appeared to be depressed in the liver. The activities of α-keto-β-methylvalerate dehydrogenase and α-ketoisovalerate dehydrogenase were also less than 10% of normal activity in liver and brain (data not shown). Enzyme activities obtained for branch-chain keto acid dehydrogenase in the control tissues were similar to those reported by Khatra et al. (5) for human tissues.

DISCUSSION

The patient suffering from a deficiency of dihydrolipoyl dehydrogenase (E_3), described in reference (8), appears also to have a defect in branched-chain amino acid metabolism. By measurement of the branched-chain keto acid dehydrogenases, we have shown that this patient has less than 10% of the normal activity exhibited by these enzymes in liver, brain, and kidney. Severe deficiency (<2% normal) at this point in the metabolism of branched chain amino acids leads to classical Maple Syrup Urine Disease (MSUD) (2,9,13), while less severe deficiency (2-8%) gives a variant MSUD with low protein tolerance, and deficiency at 8-15% gives a variant MSUD with normal protein tolerance (3,10,12). Though this patient had elevated plasma branched-chain amino acids the levels were at no time greater than 0.8 mM, which is indicative of a mild form of MSUD (6). As far as we can assess this was not a major factor in the disease process which led to his demise.

INTERPRETATION OF MULTIPLE DEFECTS IN OXIDATIVE DECARBOXYLATION

It has now been shown by us that this patient was compromised at three important sites, pyruvate dehydrogenase, α-ketoglutarate dehydrogenase (8), and branched-chain keto acid dehydrogenase. All of these enzymes for oxidative decarboxylation of α-keto-acids have a similar functional make-up consisting in each case of three main catalytic enzymes bound together in a discrete multienzyme complex. The first of these enzymes,or α-keto-acid decarboxylase (E_1),requires thiamine pyrophosphate for activity and is responsible for the decarboxylation of the carboxyl function adjacent to the ketone group. The second enzyme (E_2), or dihydrolipoyl transacetylase, has bound lipoate residues and is responsible for transferring the decarboxylated function to a coenzyme A moiety. The third enzyme (E_3), or dihydrolipoyl dehydrogenase, is responsible for transfer of reducing hydrogen from lipoate to a flavoprotein and ultimately NAD. E_1 is likely to be a different enzyme in each of the three different keto acid dehydrogenase complexes since it deals with structurally different keto acid substrates, and in inborn errors of pyruvate decarboxylase (1,4) and branched-chain keto acid decarboxylase (9) are separate entities. E_2 is also likely to be a different enzyme in each of three complexes, again because it has to deal with structurally different substrates. E_3 activity, however, involves the same substrate in all three complexes, it is deficient in our patient, and its deficiency explains all of the enzymic deletions we have demonstrated in this patient.

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15. Requests for reprints should be addressed to: Brian H. Robinson, Ph.D., Research Institute, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, M5G 1X8, Canada.

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TABLE 1

α-KETOISOCAPROATE DEHYDROGENASE (DH), α-KETOISOCAPROATE DECARBOXYLASE (DC) AND DIHYDROLIPOYL DEHYDROGENASE (E_3) IN POST MORTEM TISSUE

	KIDNEY			LIVER			BRAIN		
	nmol/min/gm tissue								
	DH	DC	E_3	DH	DC	E_3	DH	DC	E_3
Patient	0.69	0.16	117	0.80	0.19	260	0.67	0.42	80
Controls 1	4.9	0.16	2620	19.4	0.53	6120	5.9	0.51	3750
2	14.2	0.46	10800	19.6	0.90	14490	21.9	0.55	3830
3	9.1	0.25	9050	13.4	0.46	13200	5.8	0.47	2480
4	3.6	0.10	5850	12.2	0.58	7978	7.3	0.37	2570
5	3.9	0.07	-	-	-	-	4.9	0.28	-

E_3 values are transposed from reference (8).

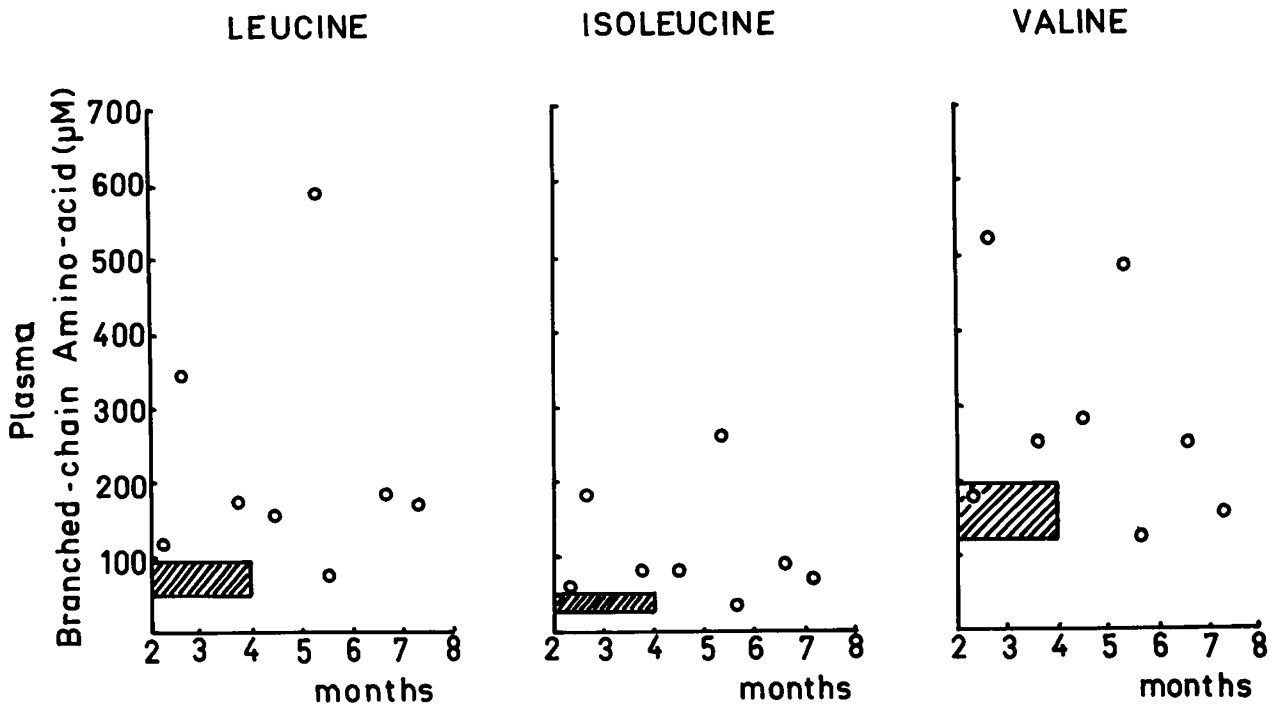

Figure 1. Levels of branched-chain amino acids in the plasma of the patient from the second month of life through to the seventh. The hatched bars indicate the range of normal values for the second to the fourth month, normal values for the fourth to the seventh month are not available.

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