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Response

To the Editor: We thank Dr McClelland and coworkers for their helpful comments to our recently published study on glutaryl-CoA dehydrogenase deficiency (1). This article already includes statistical evidence for the beneficial effect of lysine restriction in patients who were diagnosed presymptomatically (Fig. 5*A*). As clearly outlined we have used *recursive partitioning* (2) to determine predictors for categorical outcome variables, *e.g.*, acute encephalopathic crises. This statistical procedure has been chosen because it can handle numerical data that are highly skewed or multimodal, as well as categorical predictors with either ordinal or nonordinal structure. It is important to note that the division of the subgroups "Lysine restriction" ($n = 38$) and "Protein restriction or no diet" ($n = 23$) has not been made arbitrarily but is the result of this statistical analysis. This subgrouping is explained by the higher frequency of encephalopathic crises in patients receiving protein restriction (42.1%; $n = 19$) or no diet (100%; $n = 4$) compared with those receiving lysine restriction (10.5%; $n = 38$). Furthermore, we have demonstrated (Fig. 4*A, C*) the variable frequency of acute encephalopathic crises and the variable degree of disability of presymptomatically diagnosed patients in countries commonly using lysine restriction or protein restriction.

However, since the results of this study may have consequences for the current practice of metabolic centers, we have performed additional statistical analyses (Kruskal-Wallis rank sum test, Pearson's χ^2 test, Kaplan-Maier analysis) on the same dataset to stress our findings. In fact, these additional results confirm that lysine restriction is particularly beneficial for presymptomatically diagnosed patients in that it reduces the frequency of acute encephalopathic crises and the degree of disability and morbidity (Table 1). In comparison to the "lysine restriction" group patients receiving protein restriction and especially those receiving no dietary treatment had a significantly poorer outcome (Table 1). In analogy, Kaplan-Maier analysis showed significant differences in the survival rates between these dietary groups (χ (2) (2) = 27.2; $p < 0.001$). The highest survival rate was observed in the "lysine restriction" group (100% of patients). In symptomatic patients, who usually have suffered encephalopathic crises before the diagnosis has been made, lysine restriction was less effective (Table 2). Although the survival rate seemed highest in the "lysine restriction" group, Kaplan-Maier analysis showed no statistical significance between dietary groups in symptomatic patients (χ (2) (2) = 3.7; $p = 0.156$).

Lysine is the major precursor of glutxaryl-CoA, glutaric acid and 3-hydroxyglutaric acid. These dicarboxylic acids are suggested to be directly involved in the pathophysiology of glu-

Table 1. *Effect of dietary treatment on the outcome of patients being asymptomatic at diagnosis (n = 61)*

Outcome parameters	Lysine restriction ($n = 38$)	Protein restriction ($n = 19$)	No diet ($n = 4$)	Significance	Test
Encephalopathic crises (% patients)	10.5	42.1	100	$\chi^2(2) = 18.57; p < 0.001$	Chi square
Handicap score (mean pts)	0.37	1.79	3.75	$\chi^2(2) = 26.44; p < 0.001$	Kruskal-Wallis
Morbidity score (mean pts)	0.32	1.21	3.75	$\chi^2(2) = 19.34; p < 0.001$	Kruskal-Wallis

Outcome parameters were used as described before (1).

Table 2. *Effect of dietary treatment on the outcome of patients being symptomatic at diagnosis (n = 218)*

Outcome parameters	Lysine restriction ($n = 73$)	Protein restriction ($n = 110$)	No diet ($n = 35$)	Significance	Test
Handicap score (mean pts)	2.23	2.54	2.48	$\chi^2(2) = 3.96; p = 0.138$	Kruskal-Wallis
Morbidity score (mean pts)	1.47	1.87	1.86	$\chi^2(2) = 5.86; p = 0.054$	Kruskal-Wallis

Outcome parameters were used as described before (1). The frequency of acute encephalopathic crises was not included into the statistical analysis since most symptomatic patients had already had crises before the diagnosis was made.

taryl-CoA dehydrogenase deficiency (3, 4). The blood-brain barrier has a low permeability for dicarboxylic acids and thus these metabolites may accumulate in the CNS. We have hypothesized that intracerebral accumulation of dicarboxylic acids is a common pathomechanism in some organic acidurias, including glutaryl-CoA dehydrogenase deficiency. In fact, it has been demonstrated in *post mortem* studies (5, 6) and in *Gcdh*-deficient mice (7), an animal model for glutaryl-CoA dehydrogenase deficiency, that glutaric and 3-hydroxyglutaric acid strongly accumulate in the CNS. Furthermore, acute cerebral injury resembling encephalopathic crises accompanied by massive increase in glutaric acid concentrations has been induced in young *Gcdh*-deficient mice using lysine loading (8). In contrast, lysine restriction resulted in near normalization of cerebral concentrations of these metabolites in two patients (9, 10).

In conclusion, it is likely to assume that the neuroprotective effect of dietary lysine restriction is mediated *via* reduced lysine transport to the CNS and secondarily reduced intracerebral production of glutaric and 3-hydroxyglutaric acid. Since the occurrence of acute encephalopathic crises is the prognostically relevant event in this disease, the best therapeutic effect of lysine restriction is achieved when it is started *before* such crises. A prospective follow-up study has been initiated to specify the efficacy of dietary treatment in this disease (URL: http://www.metabnet.de).

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