Neurological Features and Enzyme Therapy in Patients With Endocrine and Exocrine Pancreas Dysfunction Due to *CEL* Mutations

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OBJECTIVE — To further define clinical features associated with the syndrome of diabetes and pancreatic exocrine dysfunction due to mutations in the carboxyl-ester lipase (*CEL*) gene and to assess the effects of pancreatic enzyme substitution therapy.

RESEARCH DESIGN AND METHODS — Nine patients with *CEL* gene mutation, exocrine deficiency, and diabetes were treated and followed for 30 months.

RESULTS — Treatment improved symptoms in seven of nine patients. Exocrine and endocrine function assessed by fecal elastase and A1C were not affected, although fecal lipid excretion was reduced. Vitamin E was low in all patients but increased with treatment ($P < 0.001$ at 30 months) and improved in five subjects. A predominantly demyelinating neuropathy was seen in a majority of patients, and carpal tunnel syndrome was common.

CONCLUSIONS — Pancreatic enzyme substitution alleviated symptoms and malabsorption and normalized vitamin E levels. Glycemic control was not significantly affected. The *CEL* syndrome seems associated with a demyelinating neuropathology.

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We recently described the syndrome of diabetes and exocrine pancreas dysfunction due to mutations in the carboxyl-ester lipase (*CEL*) gene (1,2). In the present study, we assessed the effects of pancreatic enzyme substitution therapy (PEST) on the endocrine and exocrine pancreatic function of mutation carriers with exocrine insufficiency. In addition, neurological features associated with the syndrome were reviewed.

RESEARCH DESIGN AND METHODS

— The patients were recruited from Family 1 in the study by Raeder et al. (1). Nine patients having diabetes and severely reduced fecal elastase level were studied. Six additional patients were included for studies of the neurological features. The patients were given standard PEST and followed for 30 months. An online appendix describes the study design, protocol, determination of exocrine dysfunction, and statistical analysis (available at http://dx.doi.org/10.2337/dc07-2217).

RESULTS

— Baseline characteristics of the nine patients are given in supplementary Table 1, and the results after treatment are shown in Fig. 1 and supplementary Table 3. Two patients dropped out of the study after 1 and 6 months, respectively, because of side effects.

Six patients identified loose stools as a major complaint. Seven patients reported immediate improvement of abdominal symptoms with treatment; however, the treatment was unsatisfactory for the majority, and doses were subsequently increased.

Baseline fecal elastase values were <10 μg/g in all patients (compatible with severe exocrine deficiency) and did not change with treatment. A1C was moderately high at baseline and did not change. Pretreatment BMI was normal (median [range] 24.0 [18–32] kg/m^2). Mean body weight increased by 3 kg after 12 months of treatment ($P = 0.01$).

Seven patients had steathorrea at baseline. At 30 months, fat excretion was reduced in all four patients studied (from 35 [25–43] to 22 [12–37] g/day; $P = 0.01$). Vitamin E levels were low in all patients but increased with treatment (from 7.6 [2.8–10.1] to 13.2 [5.5–14.1] μmol/l; $P = 0.03$) and normalized in five of seven subjects after 12 months. Levels of vitamins D and A were in the lower normal range; vitamin D levels remained unchanged, whereas vitamin A values increased with PEST (from 1.1 [0.5–1.4] to 1.6 [1.3–1.7] μmol/l; $P = 0.03$). There was a small but significant increase in total, HDL, and LDL cholesterol but no change in triglycerides. Osteoporosis was diagnosed in three and osteopenia in two patients at baseline. Bone mass density did not change.

Neurological findings

The neurological findings are described in supplementary Table 2. Electrophysiological studies revealed peripheral neuropathy with slowing of nerve conduction consistent with a demyelinating etiology in 10 of 15 subjects. Four had additional electromyogram pathology suggesting axonal damage. There was no correlation between diabetes duration and symptom severity. Five subjects had symptoms and electrophysiological signs of carpal tunnel syndrome.

Magnetic resonance imaging showed multiple high-signal lesions in the cere-

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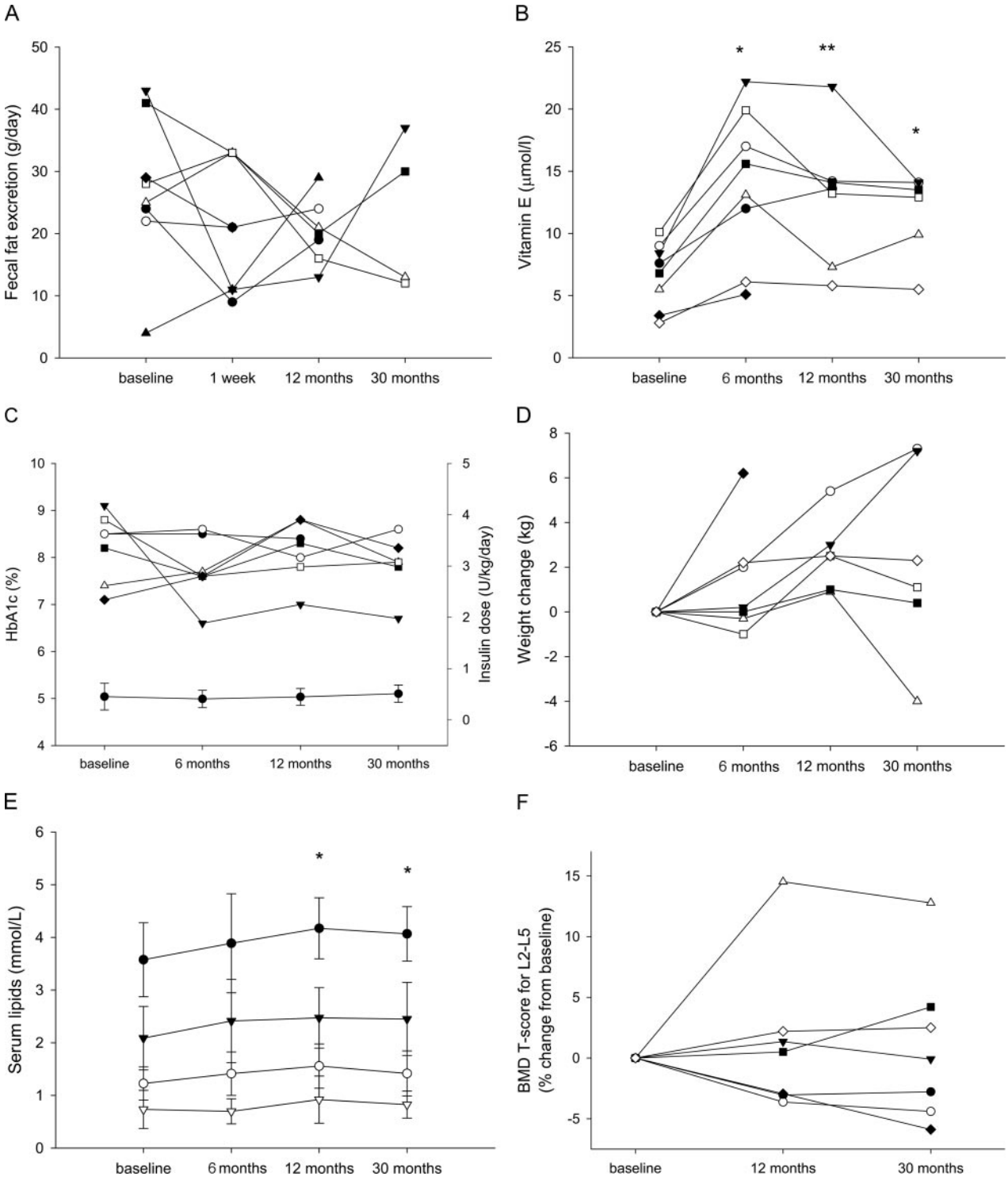

Figure 1—*Effect of PEST treatment on selected clinical variables.* A, B, D, F, *and the upper part of* C *(A1C) show development of the variables for each individual, whereas* E *and the bottom part of* C *show means ± SD.* A*: Mean 72-h fat excretion was increased at baseline (normal values <7 g/day) and showed reduction after 1 week (NS), 12 months (NS), and 30 months of treatment (significant reduction compared with baseline for the four patients delivering stool at 30 months).* B*: Serum concentrations of the fat-soluble vitamin E were below the normal range in all patients at baseline, reflecting malabsorption, but showed significant increase from baseline at 6, 12, and 30 months. *P < 0.001; **P < 0.01.* C*: Glycemic control shown by A1C was stable despite a slight but significant weight gain during treatment. The bottom of the graph (●) shows mean insulin dose per day.* D*: The absolute weight change from baseline showed interindividual variation. Some subjects experienced a substantial weight gain.* E*: All patients had remarkably low serum lipid values at baseline. There was a slight but significant increase at 6, 12, and 30 months for total (●), HDL (○), and LDL (▲) cholesterol. Triglyceride levels (△) did not change significantly. *P ≤ 0.05 for total, HDL, and LDL cholesterol at 12 months and for total and LDL cholesterol at 30 months.* F*: Bone mass density (BMD), as illustrated by* T *score for L2–L5, was increased or remained stable after 30 months of treatment in one-half of the subjects and had decreased slightly, as expected, in the others.*

bral periventricular white matter in one patient (IV-11) consistent with her multiple sclerosis diagnosis. Another subject (III-9) had scattered high-signal lesions in the supratentorial white matter, and his daughter had one periventricular high-signal lesion. They showed no clinical evidence of central nervous system disease. There was no effect on neurological symptoms after 12 months of treatment.

CONCLUSIONS — PEST constitutes the main treatment of maldigestion due to exocrine pancreatic insufficiency. Symptomatic effect in our patients was immediate, probably due to improved absorption, as indicated by decreased fecal fat excretion and normalization of serum vitamin E. It is well recognized that fat excretion is seldom normalized by PEST. Exocrine function, as assessed by fecal elastase, did not improve. This was anticipated; the very low elastase values probably reflect end-stage pancreatic disease. Glycemic control remained unchanged, confirming recent results from a study examining enzyme replacement in type 1 diabetes with exocrine dysfunction (3).

A high prevalence of exocrine insufficiency has been reported in both type 1 and type 2 diabetes (4) and in *HNF1A* and *HNF1B* maturity-onset diabetes of the young (5,6). Claims that this deficiency is moderate, nonprogressive, and therefore clinically irrelevant (7) are contradicted by the finding of pathologically high fat excretion in diabetic patients with fecal elastase deficiency (4). An independent correlation between fecal elastase levels and, respectively, glycemic control and residual β-cell function has been reported (8).

A predominantly demyelinating neuropathy was present in 10 of 15 patients. Only four patients had evidence of axonal damage. Neuropathy is common in diabetes, particularly in the presence of chronically poor glycemic control, but it is typically in the form of axonopathy (9), although demyelinating changes are described (10). Our patients exhibited few signs of long-standing hyperglycemia (supplemenary Table 1). No correlation between disease duration and presence of neuropathy was seen. Five patients had carpal tunnel syndrome, confirming the association between diabetes and compression neuropathy.

Vitamin E deficiency affects both the central and peripheral nervous systems (11). The associated peripheral neuropathy is most often axonal (11), although demyelinating neuropathy also occurs (12). Vitamin E levels improved following treatment, but the electrophysiological findings and patients' sensory symptoms did not improve. This result is consistent with that in primary vitamin E deficiency, in which supplementation, at best, stabilizes the condition. Fat malabsorption and/or chronic vitamin E deficiency may contribute to the neurological manifestations seen in Family 1.

In conclusion, demyelinating peripheral neuropathy appears to be a consistent feature of the *CEL* syndrome. Whether this is directly connected to the mutation or secondary to malabsorption and/or diabetes is unclear and warrants further study. PEST alleviated symptoms, reduced fecal fat excretion, and improved vitamin A and E status but did not improve glycemic control. Vitamin status should be checked in patients with diabetes and fecal elastase deficiency because it may indicate treatable malabsorption.

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