Protection From Clinical Peripheral Sensory Neuropathy in Alström Syndrome in Contrast to Early-Onset Type 2 Diabetes

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OBJECTIVE — Alström syndrome, with type 2 diabetes, and blindness could confer a high risk of foot ulceration. Clinical testing for neuropathy in Alström syndrome and matched young-onset type 2 diabetic subjects was therefore undertaken.

RESEARCH DESIGN AND METHODS — Fifty-eight subjects with Alström syndrome (18 insulin-resistant nondiabetic and 40 diabetic; aged 8–43 years) and 30 young-onset diabetic subjects (aged 13–35 years) were studied. Neuropathy symptom questionnaires were administered. Graded monofilament and 128-MHz tuning fork vibration perception were assessed in both feet.

RESULTS — Neuropathic symptoms, loss of monofilament, and/or vibration perception were reported by 12 of the 30 young-onset type 2 diabetic subjects (6 had neuropathic ulceration) but none of the subjects with Alström syndrome.

CONCLUSIONS — The striking preservation of protective foot sensation in Alström syndrome may provide a clue to the causes of differential susceptibility to neuropathy in the wider diabetic population.

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Alström syndrome is a rare autosomal recessive condition characterized by cone-rod dystrophy and childhood blindness, obesity and insulin resistance leading to type 2 diabetes in adolescence, and hyperlipidemia (1,2). Mutations in the *ALMS1* gene have been described in the majority of cases (3,4). The accompanying blindness might increase the risk of foot ulceration if peripheral neuropathy were to develop. Therefore, a systematic foot examination of 58 subjects with Alström syndrome and 30 young-onset type 2 diabetic subjects was undertaken.

RESEARCH DESIGN AND METHODS

— Ethics committees of Torbay Hospital, Bristol Royal Hospital for Children, and The Jackson Laboratory gave study approval. Subjects with Alström syndrome were studied at Alström Syndrome U.K. and Alström Syndrome International clinics. Fifty-eight subjects with Alström syndrome and 30 young-onset (<25 years of age at diagnosis) type 2 diabetic subjects; 10 of 12 patients from the adolescent type 2 diabetes register at Bristol Royal Hospital for Children; and 20 of 22 patients from the diabetes retinal screening register of South Devon Healthcare, Torbay Hospital were included.

Clinical protocol

A validated questionnaire (available in an online appendix at http://dx.doi.org/10.2337/dc08-1584) seeking symptoms of bilateral neuropathic pain was administered to all subjects by three trained investigators. Research-grade 2-, 4-, 6-, 8-, 10-, and 15-g monofilaments (Bailey Instruments, Manchester, U.K.) and 128-MHz tuning forks were used to test for protective sensation in subjects with eyes closed (5) (see Clinical Protocol available in the online appendix). Briefly, monofilaments were bounced to warm them up and applied firmly to six sites on each foot with a variable pause between tests to exclude false-positive responses. Calloused sites were avoided. Preservation of vibration perception was recorded if the subject sensed vibration at the tip of the hallux for 3 s and correctly identified when damped. Serum lipids and A1C were taken from patient records in the U.S. and from clinical laboratories at Torbay Hospital and Bristol Royal Hospital for Children in the U.K.

Statistics

For statistical testing, parametric ANOVA was used for BMI and A1C and the Kruskal-Wallis test was used for monofilaments. For pulses, 128 V, and reflexes, Fisher's exact test was used. Statistical computations were performed with Foundation for Statistical Computing software (R2.6.1; http://www.r-project.org). The significance threshold was set at $P \leq 0.05$.

RESULTS

— The Alström diabetic subjects ($n = 40$) and young-onset type 2 diabetic patients ($n = 30$) are well matched (Table A1 of the online appendix) except for duration of diabetes, which is longer in the Alström diabetic group: for type 2 diabetes vs. Alström syndrome diabetes, respectively, duration of diabetes 4.6 ± 3.2 vs. 13.8 ± 2.8 years; A1C 8.6 ± 2.5 vs. 9.1 ± 1.5%, $P = 0.14$; serum cholesterol 5.3 ± 0.9 vs. 6.1 ± 1.3 mmol/l, $P = 0.25$; and serum triglyceride 3.7 ± 1.9 vs. 0.8 ± 6.0 mmol/l, log-transformed $P = 0.15$. Table 1 shows the prevalence of neuropathic symptoms and loss of protective sensation in each group of subjects. No Alström syndrome subjects manifested typical neuropathic pain or absence of vibration perception. All perceived 6-g monofilament stimuli at all

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Table 1—*Significance testing between young-onset type 2 diabetic subjects and Alström syndrome subjects with diabetes*

Parameter	Alström syndrome with no diabetes	Alström syndrome with diabetes	Type 2 diabetes	Type 2 diabetes vs. Alström syndrome with diabetes (*P*)
n	18	40	30	
Neuropathic symptoms (%)	0	0	30.1	<0.0001
Perception				
all 2-g monofilament (%)	80	95	36	0.001
all 10-g monofilament (%)	100	100	38	0.001
128-MHz vibration (%)	100	97	72	0.004
Neuropathy (%)	0	0	34.6	0.0006
Foot ulceration	0	0	6	<0.0001

The Kruskal-Wallis test for monofilament perception and Fisher's exact test for 128 V (128-MHz tuning fork perception) were used. See text for definition of neuropathy and characteristics of symptoms.

sites, and >80% perceived all 2-g tests. None had present or past foot ulcers.

In contrast, neuropathic symptoms, absent vibration perception, or impairment of 6-g or 10-g monofilament perception was found in 14, 11, 7, and 12 of the control young-onset type 2 diabetic subjects, respectively. Six had neuropathic ulcers, and one had a bilateral ulcer.

Statistical analysis showed highly significant differences between Alström syndrome diabetic and young-onset type 2 diabetic patients with respect to presence of neuropathic symptoms ($P < 0.0001$), absence of vibration perception ($P = 0.004$), and mean lightest perceived monofilament ($P = 0.00001$).

CONCLUSIONS — Impairment of vibration sense and/or monofilament perception at 10 g is strongly predictive of future ulceration in diabetes (6,7). Our findings with graded monofilaments and vibration perception have confirmed the high prevalence of peripheral sensory loss, neuropathy, and ulceration in a small group of young/adolescent-onset type 2 diabetic individuals.

Alström syndrome diabetic subjects maintained good protective sensation despite comparable hyperglycemia and dyslipidemia (online appendix). This finding is encouraging, as it confirms that Alström syndrome subjects can undertake exercise and domestic activities with low risk of foot ulceration. The freedom from clinical signs of neuropathy suggests the possibility of a protective factor, associated with the syndrome, that may, when identified, increase understanding of the causes of diabetic neuropathy and suggest novel therapeutic interventions. Studies of nerve conduction in these patients are needed to confirm these findings.

Alström syndrome patients could be protected from clinical diabetic neuropathy because of their short stature (8,9), though the mean height for Alström syndrome patients was not significantly different from that for control subjects. It was recently reported that patients with Alström syndrome have subtle impairments in the growth hormone–IGF axis with a reduction in acid labile subfraction and IGF binding protein-1, whereas IGF binding protein-2 was shown to be markedly increased (10). These alterations could protect against microvascular complications as in the sex-linked form of ateliotic dwarfism (11,12).

The finding that the ALMS1 protein localizes intracellularly to the centrosome and may therefore influence microtubular function has led to speculation that transport of GLUT1–5 receptors to the cell surface may be impaired in Alström syndrome (13). Underexpression of GLUT1 receptors might protect neurons from hyperglycemic metabolic insult in those with diabetes and Alström syndrome. Further studies evaluating the roles of ALMS1 protein and microtubular function in normal neuronal function and neuropathies are strongly indicated.

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