Protection from clinical peripheral sensory neuropathy in Alström Syndrome in contrast to early onset type2 diabetes.

Short title: Protection from neuropathy in Alström syndrome

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Additional information for this article can be found in an online appendix at http://care.diabetesjournals.org.

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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, aged 8-43 years (18 insulin resistant, non-diabetic and 40 diabetic) and thirty young onset diabetic subjects aged 13-35 years were studied. Neuropathy symptom questionnaires were administered. Graded monofilament and 128MHz 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 type 2 diabetic subjects (six 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.
Alström syndrome is a rare autosomal recessive condition characterised by cone-rod dystrophy and childhood blindness, obesity and insulin resistance leading to type 2 diabetes in adolescence, and hyperlipidaemia (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
Ethical 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 UK and Alström Syndrome International clinics. Fifty eight subjects with Alström syndrome and thirty young onset (< 25 years at diagnosis) type 2 diabetic subjects, 10 of 12 from the adolescent type 2 diabetes register at Bristol Royal Hospital for Children (BRHC) UK, and 20 of 22 known from the diabetes retinal screening register of South Devon Healthcare, Torbay were included.

Clinical Protocol: A validated questionnaire seeking symptoms of bilateral neuropathic pain was administered to all subjects by three trained investigators (questionnaire is available in an online appendix at http://care.diabetesjournals.org).

1). Research grade 2, 4, 6, 8, 10, 15 gm monofilaments (Bailey Instruments, Ltd., Manchester, UK) 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 then applied firmly to 6 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 tip of hallux for 3 seconds and correctly identified when damped.

Serum lipids and haemoglobin A1c (HbA1c) were taken from patient records in the US and from clinical laboratories at Torbay and BRHC in the UK.

Statistics: For BMI and HbA1c, parametric ANOVA was used for statistical testing and Kruskal-Wallis test for monofilaments. For pulses, 128VS, and reflexes, Fisher exact test was used. Statistical computations were performed with the Foundation for Statistical Computing software R2.6.1 (http://www.r-project.org). The significance threshold was set at \( P<0.05 \).

RESULTS
The Alström diabetic subjects and young onset type 2 patients are well matched (see Table A1 available in the online appendix) except for duration of diabetes which is longer in the Alström diabetic group: duration 4.6+-/-3.2 vs 13.8+-/-2.8 yrs; HbA1c 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, \( p=0.25 \); serum triglyceride 3.7+-/-1.9 vs % .8+-/- 6.0 mmol/l log transformed \( p=0.15 \)- all type2 diabetes (n=30) vs Alström diabetes (n=40) respectively. Table 1 shows the prevalence of neuropathic symptoms and loss of protective sensation in each group of subjects. No Alström subject manifested typical neuropathic pain, nor
absence of vibration perception. All perceived 6 gram monofilament stimuli at all sites and >80% perceived all 2 gram tests. None had present or past foot ulcers.

In contrast, neuropathic symptoms, absent vibration perception, or impairment of 6, 10 gram monofilament stimuli were found in 14, 11, 7, and 12 of the 30 control young onset type2 subjects respectively. Six had neuropathic ulcers, one bilateral.

Statistical analysis showed highly significant differences between Alström 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 10g 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 hyperglycaemia and dyslipidaemia (appendix 2). This finding is encouraging as it confirms that Alström 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 which may, when identified, increase understanding of the causes of diabetic neuropathy and suggest novel therapeutic interventions. Studies of nerve conduction in these patients are indicated 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 patients was not significantly different from controls. It was recently reported that patients with Alström syndrome have subtle impairments in the GH/IGF axis with a reduction in acid labile sub-fraction and IGFBP-1 while IGFBP-2 was 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 ALMS 1 protein localises intracellularly to the centrosome and may, therefore, influence microtubular function has led to speculation that transport of glucose transporter receptors (GLUT 1-5) to the cell surface may be impaired in Alström syndrome (13). Under expression of GLUT 1 receptors might protect neurons from hyperglycaemic metabolic insult in those with diabetes and Alström syndrome.

Further studies evaluating the roles of ALMS 1 protein and microtubular function in normal neuronal function and neuropathies are strongly indicated.

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REFERENCES


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Table 1 Significance testing between 30 young onset type 2 diabetic subjects and all 40 Alström subjects with diabetes. Kruswal Wallis test for monofilament perception and Fisher’s exact test for 128VS (128 MHZ tuning fork perception). For definition of neuropathy and characteristics of symptoms see text.