Overgrowth of oral mucosa and facial skin, a novel feature of aspartylglucosaminuria

Pekka Arvio, Maria Arvio, Matti Kero, Sinikka Pirinen, Pirjo-Liisa Lukinmaa

Abstract
Aspartylglucosaminuria (AGU) is a lysosomal storage disorder caused by deficiency of aspartylglucosaminidase (AGA). The main symptom is progressive mental retardation. A spectrum of different mutations has been reported in this disease, one missense mutation (Cys163Ser) being responsible for the majority of Finnish cases. We were able to examine 66 Finnish AGU patients for changes in the oral mucosa and 44 of these for changes in facial skin. Biopsy specimens of 16 oral lesions, 12 of them associated with the teeth, plus two facial lesions were studied histologically. Immunohistochemical staining for AGA was performed on 15 oral specimens.

Skin was seborrheic in adolescent and adult patients, with erythema of the facial skin already common in childhood. Of 44 patients, nine (20%) had facial angiofibromas; tumours primarily occurring in association with tuberous sclerosis. Odemtic buccal mucosa (leucoedema) and gingival overgrowths were more frequent in AGU patients than in controls (p<0.001).

Of 16 oral mucosal lesions studied histologically, 15 represented fibroepithelial or epithelial hyperplasias and were reactive in nature. Cytoplasmic vacuolisation was evident in four. Immunohistochemically, expression of AGA in AGU patients’ mucosal lesions did not differ from that seen in corresponding lesions of normal subjects. Thus, the high frequency of mucosal overgrowth in AGU patients does not appear to be directly associated with lysosomal storage or with alterations in the level of AGA expression.

The clinical picture of AGU was described in 1972 in 34 Finnish patients \(^1\) and in 1993 in 121. \(^1\) The main symptom is progressive mental retardation; children are mildly affected and adults severely or profoundly retarded. Patients learn new skills and abilities up to the age of 13-16; after their teens they undergo gradual decline and rapid mental and somatic deterioration takes place after the age of 25-30. Patients frequently have epileptic seizures and psychiatric symptoms. They also have musculoskeletal and connective tissue abnormalities as well as inflammatory symptoms; recently, we described an increased prevalence of chronic inflammatory arthritis. \(^1\) The life span of the patients is usually under 45 years. Dysmorphic orofacial features are multifarious and include macroglossia, dental malocclusions, limited mouth opening, and small maxillary sinuses, \(^2\) as well as thick lips, gingival hyperplasia, low nasal bridge, and broad face. \(^2\) Patients’ dental health is poor with increased prevalence of gingivitis, dental caries, and odontogenic tumours. \(^2\) Sagging facial skin and infected facial acne are common features in adults. A few cases have been reported with angiokeratomas. \(^3\) \(^4\)

Here we describe increased frequencies of overgrowths and other abnormalities in AGU patients’ oral mucosa and facial skin, which represent new clinical signs of the disease.

Materials and methods
CLINICAL EXAMINATION
This investigation is part of a large project aimed at delineation of craniofacial features in AGU. The study was approved by the Ethics Committee, Institute of Dentistry, University of Helsinki. Patients were contacted via the Finnish AGU Family Society (n=47), and we also obtained permission to examine 19 middle aged patients living in nursing homes for mentally retarded persons.

Changes in oral soft tissues of 66 AGU patients (32 males, 34 females; age range 4-56, mean 23.2 years) and of 122 age and sex matched, randomly selected healthy controls were evaluated in a dental chair. For the registration we used the diagram introduced by Roed-Petersen and Renstrup. \(^2\) Many patients over 30 (11/24) had lost most of their natural teeth and two were toothless. To evaluate possible differences in oral mucosal findings between AGU patients and healthy people, the frequencies were tested with the chi-square test and Fisher’s exact test.

Dermatological examination was performed on 44 of the 66 patients (22 males, 22 females; age range 4-50, mean 23.7); we recorded...
Oral and facial overgrowth in AGU

Studied elsewhere.

† Specimen taken in association with removal of tooth.

* All gingival specimens taken from marginal gingiva.

...these specimens were also immunostained. These specimens were from the files of the Institute of Dentistry, Department of Oral Pathology, University of Helsinki, Helsinki, Finland, and had been processed in the same way as the AGU patients’ specimens. They comprised gingival, buccal, and lingual lesions, which had been histologically designated fibroepithelial hyperplasias with or without inflammatory changes.

**Preparation of tissue specimens for histological examination**

The specimens were fixed with 10% neutral buffered formalin for one to two days, dehydrated through an increasing ethanol series and xylene, and embedded in paraffin in the usual manner. A representative series of sections, 6 µm thick, were cut from each specimen and stained with haematoxylin and eosin and, to rule out candidiasis in selected cases, with the periodic acid–Schiff (PAS) method.

**Antibodies**

Rabbit antisera specific for the denatured 24 kDa AGA subunit²⁵ were obtained from Professor Leena Peltonen (National Public Health Institute, Helsinki, Finland). That staining pattern in paraffin sections of various tissues of normal subjects and AGU patients correspond to distribution patterns of AGA in vivo has already been established.²⁵

**Immunohistochemical staining**

The immunostaining procedure based on a three step peroxidase-antiperoxidase method has been previously described in detail.²⁵ Briefly, the paraffin sections were rehydrated, and to overcome the masking effect of formalin fixation on AGA antigenicity, pretreated with pepsin (Merck; Darmstadt, Germany; 0.4% in 0.01 mol/l HCl for 40 minutes at 37°C). To block any endogenous peroxidase activity in the tissues, the sections were treated with 0.3% H₂O₂ in methanol, washed with phosphate buffered saline (PBS), and stained with the Vectastain rabbit Elite kit (Vector Laboratories, Burlingame, CA, USA). The sections were then non-specifically blocked by incubation in 4% bovine serum albumin (Sigma; St Louis, MO, USA) before immunostaining with the specific rabbit antisera. The immunostaining procedure was based on a three step peroxidase-antiperoxidase method. The positive reaction was visualised using a diaminobenzidine tetrahydrochloride kit (Dako, Glostrup, Denmark).

**Histological examination**

**Patients and tissue specimens**

Biopsy specimens for diagnostic and therapeutic purposes from the oral mucosa or facial skin or both from 13 AGU patients (six male, seven female; age range 8–48 years) were available for study. The oral specimens were taken in association with gingivectomy, extraction of teeth, or removal of mucosal overgrowths. A total of 18 specimens, 16 oral and two facial, were studied. Two oral specimens each were biopsied from four patients and an oral and a facial specimen from one patient. Major clinical characteristics of the patients and the location and type of lesions are shown in table 1. None of the 12 patients submitting oral specimens received medication known to cause gingival/oral mucosal overgrowth as a side effect.

All oral specimens with the exception of one buccal overgrowth (table 1, case 6) were studied immunohistochemically for expression of AGA. For comparison, specimens from eight normal subjects (age range 15–56 years), corresponding both clinically and histologically to those taken from the AGU patients, were also immunostained. These specimens were

**Table 1 Clinical and histological features of oral and facial tissue changes of 13 AGU patients**

<table>
<thead>
<tr>
<th>Case</th>
<th>Specimen</th>
<th>Location*</th>
<th>Clinical overgrowth</th>
<th>Cytoplasmic vacuolisation</th>
<th>Inflammatory changes</th>
<th>Histopathological diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Gingiva†</td>
<td>Facial</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Epithelial hyperplasia</td>
</tr>
<tr>
<td>2</td>
<td>Alveolar mucosa †</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Fibroepithelial hyperplasia</td>
</tr>
<tr>
<td>3</td>
<td>Alveolar mucosa</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Fibroepithelial hyperplasia</td>
</tr>
<tr>
<td>4</td>
<td>Gingiva</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Fibroepithelial hyperplasia</td>
</tr>
<tr>
<td>5</td>
<td>Gingiva</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Fibroepithelial hyperplasia</td>
</tr>
<tr>
<td>6</td>
<td>Buccal mucosa</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Fibroepithelial hyperplasia</td>
</tr>
<tr>
<td>7</td>
<td>Gingiva</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Fibroepithelial hyperplasia</td>
</tr>
<tr>
<td>8</td>
<td>Gingiva</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Pseudoepitheliomatous hyperplasia</td>
</tr>
<tr>
<td>9</td>
<td>Gingiva</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Fibroepithelial hyperplasia with pseudoepitheliomatous hyperplasia</td>
</tr>
<tr>
<td>10</td>
<td>Tongue</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Fibroepithelial hyperplasia</td>
</tr>
<tr>
<td>11</td>
<td>Facial skin</td>
<td>Yes</td>
<td>Not analysed</td>
<td>Yes</td>
<td>Yes</td>
<td>Fibroepithelial hyperplasia</td>
</tr>
<tr>
<td>12</td>
<td>Gingiva</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Fibroepithelial hyperplasia</td>
</tr>
<tr>
<td>13</td>
<td>Buccal mucosa</td>
<td>Yes</td>
<td>Not analysed</td>
<td>Yes</td>
<td>Yes</td>
<td>Fibroepithelial hyperplasia with epithelial disintegration</td>
</tr>
</tbody>
</table>

* All gingival specimens taken from marginal gingiva.
† Specimen taken in association with removal of tooth.
‡ Studied elsewhere.
Burlingame, CA, USA) according to the instructions of the manufacturer. Antisera to AGA were used at a dilution of 1:500 in PBS. The peroxidase precipitate indicating AGA immunoreactivity was made visible by the AEC staining method. Brief counterstaining of the sections with haematoxylin facilitated the correlation of the immunoprecipitate with tissue structures. To confirm the specificity of the staining results, rabbit preimmune serum and PBS were substituted for the specific AGA antisera.

Results

Clinical Findings

The prevalences of oral mucosal lesions in the AGU patients and the controls are presented in table 2. Of the 66 AGU patients, 15 (23%), but none of the control subjects, had extensive gingival overgrowths clinically designated oral fibromatosis (fig 1). The lesions were usually not directly connected to the inflamed marginal gingiva and were classified separately from the oedematous hyperplasia associated with gingivitis (fig 2). The contour of fibromatous lesions was striped or papular. The frequencies of the gingival lesions showed no sex differences and were similar in patients taking and not taking medication. The youngest patient with oral fibromatosis was an 11 year old boy. Gingival overgrowths in the tooth-bearing area were less frequent in toothless patients than in patients with their natural teeth; only three had small overgrowths in the toothless mucosa. In addition, one woman had an overgrowth in the tongue (case 10, table 1) and another in the buccal mucosa (case 13, table 1). Oedematous buccal mucosa (table 2), clinically designated leucoedema, was cobblestone-like or appeared wrinkled or lamellar (fig 3). White areas were visible in the oral mucosa of six patients (table 2). Two had homogeneous leucoplasia in the buccal mucosa, four had stripes, and one had a lichen planus-like change. Furthermore, two patients had solitary, whitish, plaque-like lesions, three had enlarged lingual papillae, one a plicated, hyperplastic tongue, and one had red pile-like hyperplasia on the ventral surface of the tongue.

Characteristics of the facial skin of the AGU patients are presented in table 3. In childhood the characteristic skin abnormality appeared as rosy cheeks. At puberty the skin became seborrhoeic. In 11 adolescent patients seborrhoea appeared as mild or papulocystic acne, and in six out of 21 patients aged >20 years old (29%) as acne rosacea. Of 44 patients, eight (aged 17-48) had facial skin overgrowths. Four had single nodules and four had large tumour-like areas (figs 4 and 5), with one patient having similar overgrowths on her shoulders. The youngest patient with such skin lesions was a 17 year old girl. Biopsy specimens taken from large, facial lesions of two patients were histologically diagnosed as an infected fibroepithelial polyp (possibly angiofibroma; case 11, table 1) and an angiofibroma (case 12).

Of the 44 patients, four had subcutaneous tumours, seven angiokeratomas, and four haemangiomas in locations other than the face.

Histological Findings

The clinical characteristics and histological diagnoses of the facial and oral lesions are summarised in table 1. The polypoid facial angiofibroma (case 12, table 1) was covered by a slightly hyperkeratinised epidermis. The tex-
ture of the dermis varied and was loose, particularly in the central part of the lesion. Characteristically, vascularity was increased (fig 6). All 16 oral mucosal lesions studied were reactive in nature. Fifteen lesions were designated as fibroepithelial (10 specimens) or epithelial (five specimens) hyperplasias and one leucokeratosis. Those mucosal lesions in which both the surface epithelium and the connective tissue compartment contributed to an overgrowth, which was also evident clinically, were diagnosed as fibroepithelial hyperplasias. Those specimens showing thickening of the surface epithelium in histological examination but clinically not necessarily appearing as overgrowths were designated epithelial hyperplasias. Of the 16 lesions, nine appeared histologically similar to clinically corresponding overgrowths from normal subjects (fig 7A).

Disintegration and acantholysis of the squamous surface epithelium of both buccal lesions biopsied from case 13 (table 1) made them resemble lesions seen in pemphigus vulgaris (fig 7B). However, consistent with the absence of any clinical signs, routine diagnostic immunofluorescence examination of frozen sections of another biopsy specimen from the buccal mucosa ruled out the presence of pemphigus. All 12 gingival/alveolar mucosal lesions showed chronic, mononucleate inflammatory cell infiltrate, frequently with plasma cell predominance. Cytoplasmic vacuolisation, histologically characteristic of AGU, was seen in the connective tissue compartment of four gingival/alveolar mucosal specimens (fig 7C), with an age effect (table 1). In addition, an 8 year old boy (case 1, table 1) showed peculiar globular structures in the connective tissue compartment of the gingival lesion (fig 7D). Except for the changes in gingival and buccal specimens taken from case 6, all lesions derived from any one patient appeared alike.

**Table 3 Clinical changes in facial skin in 44 patients with AGU**

<table>
<thead>
<tr>
<th>Group</th>
<th>Under 15 y (n=13)</th>
<th>15-29 y (n=14)</th>
<th>30 y and over (n=17)</th>
<th>Total (n=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema</td>
<td>7</td>
<td>10</td>
<td>12</td>
<td>29 (66)</td>
</tr>
<tr>
<td>Seborrhea</td>
<td>1</td>
<td>11</td>
<td>15</td>
<td>27 (61)</td>
</tr>
<tr>
<td>Atopy</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Angiofibroma</td>
<td>0</td>
<td>3</td>
<td>6*</td>
<td>9 (20)</td>
</tr>
</tbody>
</table>

* Including one patient with similar lesions only on her shoulders.

**Immunoreactivity of AGA**

No consistent differences were found in the staining patterns or intensities for AGA between the corresponding mucosal lesions of the normal subjects and of patients with AGU; staining results are thus described together. With the exception of the keratinised surface layer, the mucosal squamous epithelium showed weak to moderate immunoreactivity. Fibroblasts stained and in the case of non-
inflamed lesions clear reactivity was also seen in the capillary endothelial cells (fig 7E, F). The overall AGA reactivity in the connective tissue compartment of the lesions of both the normal subjects and AGU patients increased with the inflammatory cell infiltrate. At the same time the staining pattern became diffuse. Cytoplasmic vacuolisation in the AGU pa-

Figure 7  Histological appearance (A-D) and immunohistochemical staining for AGA (E-H) on paraffin sections of oral mucosal overgrowths of a normal subject (A, E) and AGU patients (B-D, F-H). Mucosal squamous epithelium is indicated by e, and ct stands for connective tissue. Case numbers refer to table 1. (A) Lingual fibroepithelial hyperplasia in a healthy subject aged 56 and (B) a buccal overgrowth from case 13 aged 47 appear similar except for the epithelial disintegration resulting in a suprabasal cleft (arrows in B) in the AGU specimen. (C) Clear cytoplasmic vacuolisation (arrows) is seen in gingival inflammatory hyperplasia from case 7 aged 32. (D) Globular accumulations (arrows) are evident in gingival inflammatory hyperplasia from case 1 aged 8. Immunostaining patterns for AGA in the normal subject (E, specimen as in A) is similar to that seen in AGU (F, specimen as in B). Epithelium stains with a weak to moderate intensity, fibroblasts (small arrows in E and F) are also faintly reactive and capillary endothelial cells (large arrows in E and F) stain clearly. (G) Despite the cytoplasmic vacuolisation (seen in C) the overall AGA immunoreactivity is intense albeit diffuse in the gingival inflammatory hyperplasia (specimen as in C). (H) No staining is seen in a section treated with AGA preimmune serum and corresponding to that seen in B and F. Haematoxylin and eosin stain (A-D). Haematoxylin counterstain (E-H). Bars=75 µm in A, B, E, F, and H, 50 µm in C and G, and 30 µm in D.
tients’ specimens did not decrease AGA reactivity (fig 7C, G). Treatment of the sections with AGA preimmune sera and PBS resulted in negligible staining (fig 7H).

Discussion

AGU is a generalised disease with symptoms expressed in various organs. Early reports in the 1970s show a characteristic patient appearance. We describe here various abnormalities of AGU patients’ oral mucosal and facial skin; the majority of their mucosal and cutaneous changes appeared clinically as overgrowths and represented oral fibromatosis and fibroepithelial hyperplasias, with or without inflammation, and angiofibromas, respectively.

The facial angiofibromas appeared in the teen years and were numerous and large in middle age, thus progressing with the general course of the disease. Gingival overgrowths, on the other hand, did not follow the same course. Patients with oral fibromatosis all had more or less complete permanent dentition; lesions were not seen even in middle aged patients who had lost most of their natural teeth. Therefore, the occurrence of gingival fibromatosis appears to be related to retention of teeth rather than to the patients’ age and disease progression. Although the patients have swallowing and speech disorders, the oral fibromatosis did not seem to exacerbate the oral condition. Since they are seriously ill, the importance of facial angiofibromas and acne is mostly aesthetic. However, the large papules may become inflamed and bleed, requiring surgical treatment. Compared to the prevalence of rosacea in the adult Swedish population (81/809), the crude relative risk for rosacea in AGU patients was 2.9 (95% confidence interval 1.4-5.8).

We saw facial angiofibroma- or angiookeratoma-like lesions in nine patients and we found benign tumours elsewhere in the skin of 14 patients. Altogether, 18 (40%) of the 44 patients examined for skin lesions had cutaneous or subcutaneous tumours. We have shown previously that AGU patients have a slightly increased frequency of odontogenic tumours. Furthermore, middle aged women have hyperplasia of the labia and nipples, and two of our patients had a history of more severe neoplasms. One woman had her mandible partially resected at the age of 34, because of a large giant cell tumour, and one boy had his testis resected at the age of 7, because of rhabdomyosarcoma. Therefore, with regard to clinical examination of AGU patients, the possibility not only of hyperplasia but also of more severe neoplasms should be kept in mind.

Increased frequencies of oral fibromatosis and facial angiofibromas, which are both reactive in nature, have been considered characteristic of tuberous sclerosis, another genetic disease, in which the patients develop various hamartomas mostly formed of proliferating haemangioblasts and fibroblasts. Unlike the extensive oral overgrowths associated with tuberous sclerosis, those seen in AGU patients are difficult to interpret by the general pathogenetic mechanism of the disease. This is also the case for the facial lesions comparable to the oral overgrowths. We are under the impression that both the oral and facial overgrowths are milder in AGU than in tuberous sclerosis. Whereas facial angiofibromas were not seen in AGU patients younger than 15 years, and their frequency did not exceed 20%, the frequency of facial angiofibromas in tuberous sclerosis has been found to increase dramatically after the age of 5 years, reaching 81% and 86% in age groups 5-14 years and 15-29 years, respectively.

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AGA is a household type of enzyme present in small amounts in all tissues. Whereas the mRNA levels in different tissues are fairly stable, the expression of the protein shows clear cell specificity. The strongest immunoreactivities have been found in the pyramidal cells of the cerebral cortex, in hepatocytes, and in the proximal tubular cells of the kidney. This implies that the level of regulation of AGA expression is post-translational rather than transcriptional. Cytoplasmic vacuolisation, serving as a light microscopic hallmark of lysosomal storage, has been observed in a variety of tissues and cell types. Consistent with the most dramatic clinical sign of AGU, progressive mental retardation, reduction in AGA levels, accompanied by cytoplasmic vacuolisation, is most striking in the pyramidal cells. We saw characteristic cytoplasmic changes, detectable by light microscopy, in only four (three cases) out of the 16 oral mucosal specimens from 12 AGU patients. All four specimens were associated with the inflamed marginal gingiva. The age range of the patients was 32-44 years, indicating that such changes in oral tissues are associated with age, as is also the case in certain functionally highly specialised cell types such as pyramidal cells and hepatocytes. Whereas all four gingival specimens showing cytoplasmic vacuolisation presented as overgrowths, all overgrowths did not exhibit vacuolisation. This suggests that in AGU there is no direct cause and effect relationship between lysosomal storage and gingival overgrowth.

Cell function and matrix composition of AGU tissues are profoundly altered. The ultrastructure of skin collagen fibres of AGU tissues are profoundly altered. The ultrastructure of skin collagen fibres of AGU patients is aberrant, and corresponding to the low levels of the protein products synthesised by AGU fibroblasts in culture, the steady state mRNA concentrations for types I and III collagen are markedly reduced. Conversely, diverse changes have been observed in the mRNA levels for collagen associated proteoglycans, also reflected in the amounts of corresponding proteins. The basically low levels of AGA in the oral mucosa may not allow even a minor decrease in the expression levels of AGA, which remains beyond the level of detection of immunohistochemistry, without resulting in altered cell function manifesting as overgrowth. Therefore, tissues even with normally low AGA levels could be particularly suscepti-
ble to an altered reaction to various stimuli. A consistent feature of the gingival changes in AGU patients, studied immunohistochemically, was chronic inflammation. For some unknown reason, gingival tissue is prone to react to different chemical stimuli, for example, to hydantoin and cyclosporin, by exuberant overgrowth.33 However, because patients with good oral hygiene do not necessarily develop gingival enlargement, such a mode of reaction appears to be modified by the inflammation. Since none of the patients who submitted oral biopsy specimens received medication known to lead to gingival overgrowth, the stimulus for the oral mucosal changes could have been the altered tissue metabolism in combination with inflammation.

Taken altogether, AGU patients have a characteristic oral anatomy with macroGLOSSIA, malocclusions, widely spaced dental arches,20 and mucosal leucoedema, as well as gingival fibromatosis and less extensive overgrowths. Whereas the high frequency of their gingival overgrowth cannot be directly explained by alterations in expression of AGA or by its consequences such as lysosomal storage, their gingival changes in particular could be an exuberant reaction to inflammation, modified by their basically abnormal tissue metabolism. The U-shaped face with broad mandible (P Arvio et al, unpublished data), low and convex profile of the nose,19 and erythematous skin are already evident in childhood. In puberty, the skin becomes seborrhoic with acne varying from mild to papulocystic. Middle aged patients have sagging skin,15 and may also suffer from rosacea or angiofibromas. Thus, whereas the facial features coarsen with age and the general progression of the disease, the gingival overgrowth appears to be associated with retention of teeth.

We are grateful to the Finnish AGU patient society and to Pirjo Hartikainen for taking an interest in this study. We thank Hannu Kautiainen for performing the statistics, Dr Ritta Aho for making the histological diagnoses of the von Leijenhorst and Professor Leena Peltonen (National Public Health Institute, Helsinki, Finland) for donating the AGA antibodies. The skilful technical assistance of Ms Sira Kylönen and Mrs Marjatta Kivekas is acknowledged. This study was supported by the Pajajarvi Rehabilitation Centre, Runeberg Research Foundation, and Ulla Helt Memorial Fund awarded by the Foundation for Paediatric Research.

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*J Med Genet* 1999 36: 398-404
doi: 10.1136/jmg.36.5.398

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