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ORIGINAL ARTICLE

What is the burden of living with autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED) in 2012? A health-related quality-of-life assessment in Finnish patients

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Summary

Objective Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED) is a rare disorder responsible for chronic candidiasis, a wide variety of autoimmune disorders and a risk of squamous cell carcinoma of the oral cavity or oesophagus. We investigated the impairment of quality of life in our cohort of Finnish patients.

Subjects, design and measurement In a postal survey, 26 patients with APECED responded to three self-reported health-related quality-of-life questionnaires: RAND-36 (general health), RBDI (depression) and DLQI (dermatology life quality index).

Results General health and vitality were the most affected items in our cohort. Male subjects presented higher impairment in emotional role limitations, social functioning, bodily pain, general mental health/emotional well-being, energy/vitality and general health perceptions but without reaching statistical significance. The number of accumulated diseases in APECED was not associated with lower results. But, age and duration of APECED correlated with fatigue ($P = 0{\cdot}01$), well-being ($P = 0{\cdot}02$) and general health ($P = 0{\cdot}03$) impairment. Depressive symptoms affected 29% of the patients. There was a statistical negative correlation between RBDI score and age and duration of APECED. Hair loss, alopecia areata universalis especially, affected more severely the quality of life of female patients. Vitiligo and candidiasis did not have any significant impact on both the genders.

Conclusions We report the first study on specific impairment of quality of life related to APECED in a cohort of adult Finnish patients. General health, emotional well-being and vitality were the most diminished aspects of quality of life in our cohort. However, our results will need to be confirmed by additional controlled studies.

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Introduction

Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED, OMIM 240300) or autoimmune polyendocrine syndrome type 1 (APS1) is a rare autosomal recessive disorder. It is caused by mutations in the *AIRE* (autoimmune regulator) gene, located on chromosome 21 (21q22·3).[1–4] Because of a founder effect, it is most prevalent in Finland (1/25 000),[5] but is observed elsewhere, too.[6–8] It associates various endocrine autoimmune disorders including mainly Addison's disease (AD), primary hypoparathyroidism (HP), primary hypogonadism, type I diabetes and hypothyroidism. Patients often develop additional nonendocrine autoimmune diseases such as alopecia areata, vitiligo, autoimmune gastritis, pernicious anaemia, hepatitis, nephritis and keratitis. Also, the patients typically develop early in life chronic mucocutaneous candidiasis (CMC), whose chronic inflammation can later in life lead to oral/oesophageal squamous cell carcinoma.[1–3]

Chronic endocrine disorders are known to impair quality of life (QoL) of the patients. This has been shown for AD,[9,10] but also in association with thyroid disorders [11] and diabetes type I, in the young.[12] However, patients with APECED not only cumulate multiple endocrine disorders, which need daily oral and lifelong hormonal replacement therapy but APECED may affect the QoL of the patients in numerous ways (Fig. 1). Life-threatening situations during APECED include adrenal crisis, sepsis due to asplenia or to immunosuppressive therapy, fulminant autoimmune hepatitis and mucosal squamous cell carcinoma. APECED may also cause great psychosocial burden. The persistent risk of developing new, possibly life-threatening

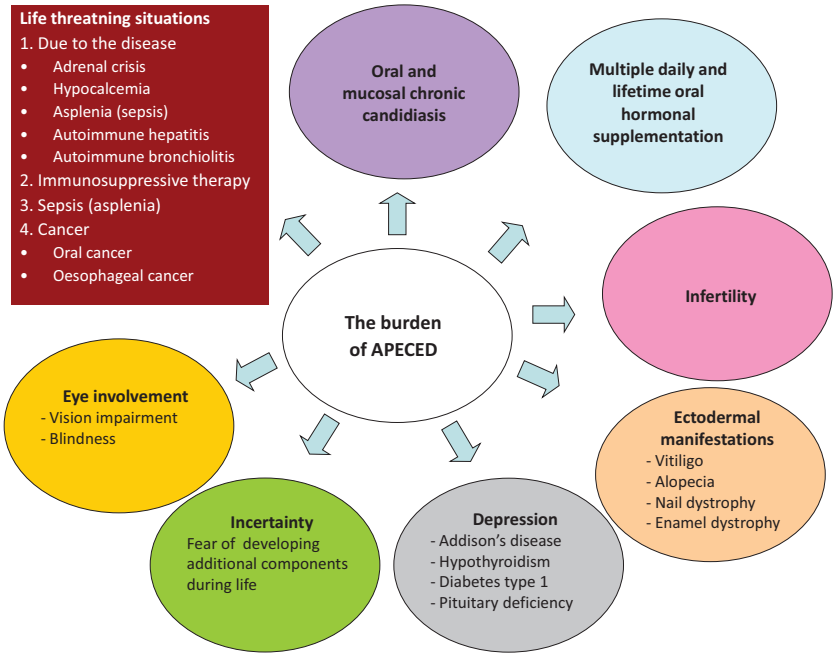

Fig. 1 The multiple facets of the burden of APECED

disease components, a personal experience when other members of the family have died from the disease, and the disfiguring aspect of cutaneous diseases (vitiligo, patchy alopecia areata, alopecia areata universalis, nail dystrophy) can be a source of continuous distress. Oral candidiasis requires strict control, sometimes continuous medication. Besides, teenage patients often deny their disease and neglect therapy, sometimes with life-threatening consequences. Based on his own long experience on patients with APECED, Perheentupa reported that depression and suicidal thoughts were not infrequent.[2] In Finland, almost all Finnish patients with APECED are nowadays members of a patient association founded in 1995 (the Finnish APECED and Addison registered association), which provides peer-support and information to the patients in the form of regular meetings, distribution of information leaflets and a web page (http://www.apeced.org). The association also has a permanent support person for eventual crises, trained by the Finnish Red Cross.

The currently available data on the impact of APECED on the quality of life are practically nonexisting. Recently, Storz *et al.* reported the burden of APS type 2 (consisting of AD and autoimmune thyroid disease or type 1A diabetes) patients in a German cohort [13] and showed a reduced physical, emotional and psychosocial well-being in these patients.[13] APS 2 patients share several common features with APS 1 patients. However, the APS2 patients develop the disease at an older age and do not suffer from candidiasis for instance and are neither at risk for oral cancer. Løvås *et al.* analysed 9 patients with APECED in their series of AD patients and showed impairment in the quality of life.[14]

We conducted a survey to investigate the impairment of health-related quality of life (HQoL) in our cohort of Finnish patients with APECED in an analytical epidemiology study using three self-reported HQoL questionnaires and special emphasis on cutaneous manifestations of chronic dermatoses such as mucosal candidiasis, alopecia or vitiligo, which also impair *per se* the QoL, especially in women.

Material and methods

Design and patients

We recruited 27 patients with confirmed APECED syndrome and *AIRE* mutation. All were aged over 16 years and unrelated. Children were excluded from the study. As the Finnish patient group has a history of willingly participating in research of their disease, the study recruitment and contact information was collected with the help of the APECED patient's association. All patients were members of the Finnish APECED and Addison registered association (APECED ja Addison Ry, http://www.apeced.org). The study was conducted in the Hospital District of Helsinki and Uusimaa, Finland, but the patients were originating, diagnosed and currently followed-up all over Finland in their local or University hospitals.

Approval for the study was obtained from the Medicine Ethical Review Board of Helsinki and Uusimaa Joint Authority (dnro 8/13/03/01/2009, research permission IAS09 APS1 6209/T101060071), and each participant signed an informed consent.

Methods

The survey was performed using three self-reported questionnaires, for which a Finnish translation has been validated: the RAND-36, the Raitasalo's modification of the short form of the Beck Depression Inventory–BDI (RBDI) and the Dermatology Life Quality Index (DLQI).

The RAND-36 is one of the most widely used HQoL survey instruments in the world today. It is a self-rated, profile-based

HQoL measure and originates from the Medical Outcomes Study 36-item short-form health survey. It is comprised of 36 items that assess eight health concepts: physical functioning (10 items), physical role limitations (four items), emotional role limitations (three items), social functioning (two items), bodily pain (two items), general mental health/emotional well-being (five items), energy/vitality (four items) and general health perceptions (five items). We used the Finnish version [15] of the RAND-36 as it has shown to have good reliability and construct validity in the Finnish general population.[15] The RAND-36 is scored in two steps. Each item is first scored on a scale from 0 to 100 (a higher score defining a higher HQL), and an average value is calculated for each of the eight dimensions. If more than 50% of the items in a dimension are missing, the average value cannot be calculated.[16]

The RBDI mood questionnaire [17–19] is a self-reported questionnaire that has been used in Finland for the past 30 years for depression. This Finnish-modified version of Beck's 13-item depression scale has 13 questions for depression. Depression is measured based on the 13 items scoring from 0 to 3, and score ranges from zero to 39 points. Five to seven points refer to mild depression, 8–15 points to moderate depression and over 16 points to severe depression.

The DLQI® is the first dermatology-specific quality-of-life instrument and the most frequently used instrument in studies of randomized controlled trials in dermatology.[20] It is a simple 10-question validated questionnaire that has been used in 33 different skin conditions and is available in Finnish.[21] Patients responded based on the symptoms they may have presented the previous week to permit accurate recall. Each question has four possible answers for a maximum of three points and a total maximum score of 30. Higher score indicates more severely affected QoL. The patients were given three different DLQI questionnaires to assess the differential effect of alopecia, vitiligo and CMC. Zero to 1 score means no effect on the patient's life, 2–5 a small effect, 6–10 a moderate effect, 11–20 a very large effect and 21–30 an extremely large effect.Questionnaires were not anonymous for the purpose of enabling comparison with a previously generated recent clinical database of APECED patients, including demographic data (gender, age, age at APECED diagnosis, age at first onset of symptoms), clinical symptoms, autoimmune endocrine and nonendocrine diseases and occurrence of oral carcinoma or other malignancies. Neither baseline hormone levels nor organ-specific auto-antibodies were analysed for this study.

The questionnaires were mailed along with an explanatory letter and informed consent and prepaid envelope for return of the questionnaire. In case of no response, patients were contacted a second time by phone (MJ). Data were then collected and analysed by NK and MJ.

Statistical analysis

Statistical analysis was conducted with NCSS 2007. Patients' characteristics were presented using median and mean and SD for continuous variables and frequencies and proportions for categorical variables. Patients' characteristics were compared using Fisher's exact test for categorical variables and Mann–Whitney *U*-Test for continuous ones. Spearman's rank correlation coefficient was applied for age, age at diagnosis, duration of the disease, total RBDI scores and RAND-36 items. Pearson correlation coefficient was a measure of the correlation between variables. Statistical significance threshold was set at $P < 0{\cdot}05$.

Results

Demographic data and clinical manifestations

Of the 27 patients, 26 returned the questionnaires (response rate 96%). Of the respondents, 19 were women (74%) and 7 men (26%), with a median age of 41·3 ± 12·3 (range 17–65). There was no statistical difference between the age of male (mean age 42·6 ± 12·1; range 30–65) and female patients (40·8 ± 12·6; range 17–57). APECED was diagnosed mainly during childhood, at a mean age of 6 years ± 4·7 (range 1–19). APECED in males was diagnosed at a slightly older aged compared to females: 8 ± 6·8 (range 1–19) *vs* 6 ± 3·8 (range 2–15), respectively (statistically not significant). The mean average duration of APECED was 35·9 years ± 10·7 (range 13–52). The clinical manifestations are summarized in Table 1. Briefly, the main manifestations included CMC (92%, 24/26), HP (84%, 22/26), AD (81%, 21/26) and ocular manifestations (77%, 20/26, including red eyes, inflammation, dry eye, assessed keratitis). The complete triad (CMC, HP and AD) was present in 65% (17/26) of the patients. The dyad was present in 31%, divided between 15·5% (4/26, CMC + HP), 11·5% (3/26, CMC + AD) and 4% (1/26, HP+AD). Only one patient had CMC as the sole clinical symptom (4%). One patient developed a squamous cell carcinoma of the tongue related to chronic oral candidiasis during the course of the disease (4%, 1/26). Overall, patients presented between 1 to 10 disease components of APECED. Fifty-eight per cent had five or less components, while 42% had six or more components of the disease. Less than a third (27%, 7/26) had three components. RAND-36 and RBDI were filled in all cases, but one RAND-36 was incomplete. DLQI questionnaires were filled in by all the patients with vitiligo (3/3) and hair loss/alopecia (11/11) and by 95% (21/22) of the patients with a past or present history of CMC. Lastly, five patients were active smokers (5/26, 19%). Alcohol intake or drug abuse was not investigated in the present study.

Subjective health status assessed by RAND-36

The RAND-36 scores are given in Tables 2 and 3. Overall, general health and vitality were the most affected items. Male subjects compared to female subjects scored lower results in six of eight dimensions: emotional role limitations, social functioning, bodily pain, general mental health/emotional well-being, energy/vitality and general health perceptions. The male patients scored higher only for physical-related items (physical functioning and physical role limitations). However, there was no statistically significant difference using Mann–Whitney *U*-Test for the gender. Spearman correlation failed to show any link between any of the RAND-36 item and the number of clinical disease manifestations

Table 1. Prevalence of clinical manifestations in the present Finnish APECED patients series

	Overall	Male	Female	$P < 0{\cdot}05$
n	26	7 (26%)	19 (74%)	
Age	41·3 ± 12·3	42·6 ± 12·1	40·8 ± 12·6	NS
Age of onset	6 ± 4·7	8 ± 6·8	6 ± 3·8	NS
Duration of APECED	35·9 ± 10·7	37 ± 8	36 ± 8	NS
Symptoms				
Keratoconjunctivitis	77% (20/26)	66% (4/7)	84% (16/19)	NS
Gastrointestinal dysfunction	54% (14/26)	66% (4/7)	52% (10/19)	NS
Chronic diarrhea, constipation or abdominal pain				
Mucosal candidiasis	92% (24/26)	100% (7/7)	89% (17/19)	NS
Past or active history of mucosal candidiasis (oral, vaginal)				
Vitiligo	11% (3/26)	16% (1/7)	10% (2/19)	NS
Alopecia areata/totalis	42% (11/26)	71% (5/7)	31% (6/19)	$P = 0{\cdot}068$
Hypoparathyroidism	84% (22/26)	71% (5/7)	89% (17/19)	NS
Addison's disease	80% (21/26)	100% (7/7)	74% (14/19)	NS
Hypothyroidism	42% (11/26)	43% (3/7)	42% (8/19)	NS
Type 1 diabetes	19% (5/26)	43% (3/7)	10% (2/19)	NS ($P = 0{\cdot}054$)
Pernicious anaemia	11% (3/26)	0% (0/7)	16% (3/19)	NS
Testosterone failure	14% (1/7)	14% (1/7)	NA	NA
Ovarian failure	61% (11/18)	NA	66% (11/18)	NA
Pituitary failure [Growth hormon deficiency]	23% (6/26)	28% (2/7)	21% (4/19)	NS
Asplenia	34% (9/26)	14% (1/7)	42% (8/19)	NS
Autoimmune hepatitis	4% (1/26)	14% (1/7)	0% (0/19)	NS
Nephritis	4% (1/26)	0/7	5% (1/19)	NS
Oral squamous cell carcinoma	4% (1/26)	0/7	5% (1/19)	NS

NA, not applicable; NS, not significant ($P > 0{\cdot}05$).

(Pearson's r ranging from $r = -0{\cdot}298$, $P = 0{\cdot}147$ to $r = 0{\cdot}009$, $P = 0{\cdot}964$). The comparison between patients with AD and type I diabetes (5/21) *vs* those with only AD (21/26) did not show any significant differences (Mann–Whitney test, $P > 0{\cdot}05$). However, both age and duration of the disease were associated with fatigue (age: $r = 0{\cdot}468$, $P = 0{\cdot}01$; and duration: $r = 0{\cdot}48$, $P = 0{\cdot}01$), well-being (age: $r = 0{\cdot}74$, $P = 0{\cdot}02$; duration: $r = 0{\cdot}459$, $P = 0{\cdot}02$) and general health (age: $r = 0{\cdot}431$, $P = 0{\cdot}04$; duration: $r = 0{\cdot}450$, $P = 0{\cdot}03$). Besides, fatigue, vitality, well-being, social functioning and general health displayed positive correlation according to Spearman's test ($P < 0{\cdot}05$, Table 3). There were no significant differences between smokers and nonsmokers for any of the RAND36 scores (Mann–Whitney analyse $P > 0{\cdot}05$).

Subjective mental health as assessed by RBDI

The mean total RBDI score was 3 ± 4·1 (0–16). Male patients had slightly higher scores than female patients (mean score of 3·4 *vs* 2·8). However, these differences were not significant. Eight patients scored over five: six had mild depressive symptoms (score 5–7), one had moderate depressive symptoms (score 8–15) and one had severe depressive symptoms. Four patients acknowledged taking currently anti-depressive treatments on a regular basis. Among these were the two patients with moderate or severe depressive symptoms (13 and 16) but also two patients who scored 0. The highest mean score was obtained for the question regarding sleeping disturbances with a mean score of 0·6 (0·4 for men and 0·6 for women). There was no statistical association between RBDI score and any of the clinical manifestations, neither with the number of manifestations ($r = 0{\cdot}006$, $P = 0{\cdot}973$). The comparison between patients with AD and type I diabetes (5/21) *vs* those with only AD (21/26) did not show any significant differences for total RBDI score (Mann–Whitney test, $P > 0{\cdot}05$). Spearman correlation showed a statistical negative correlation between total RBDI and elevated age ($r = -0{\cdot}404$, $P = 0{\cdot}04$) as well as long duration of APECED ($r = -0{\cdot}454$, $P = 0{\cdot}02$), but no relation with the age at first onset of the disease ($r = 0{\cdot}130$, $P = 0{\cdot}525$). There was a negative correlation between RBDI scores and fatigue ($r = -0{\cdot}680$, $P = 0{\cdot}0002$), well-being ($r = -0{\cdot}451$, $P = 0{\cdot}02$), social ($r = -0{\cdot}414$, $P = 0{\cdot}04$) and general health ($r = -0{\cdot}585$, $P = 0{\cdot}003$). There were no significant differences between smokers and nonsmokers (Mann–Whitney test $P > 0{\cdot}05$).

Effect of skin symptoms on the Quality of Life (DLQI)

DLQI scores were analysed separately according to each skin symptom. Three patients had vitiligo and their mean DLQI score was 0·6 (0–2). Two patients scored 0 (no effect on patient's QoL), while the third one scored two (small effect on patient's QoL).

Eleven patients with alopecia areata or hair loss responded to the DLQI questionnaire. Their mean score was 1·9 (0–7), show-

Table 2. RAND 36 scores in the present Finnish APECED patients series

	Total (n = 26) (minimum and maximum scores)	Male (n = 7)	Female (n = 19)	Mann–Whitney $P < 0{\cdot}05$
Physical functioning	86 ± 21·3 15–100	89·3 ± 18·1	84·7 ± 22·6	NS
Physical role limitations	87·5 ± 23·7 0–100	89·3 ± 13·4	86·8 ± 26·8	NS
Emotional role limitations	89·10 ± 21·5 33·3–100	80·9 ± 26·2	92·1 ± 19·5	NS
Energy/vitality	60 ± 20·4 20–100	48·6 ± 20·9	64·4 ± 18·9	NS
General mental health/emotional well-being	73·9 ± 20·2 20–100	60·5 ± 25·1	79·1 ± 15·9	NS
Social functioning	81·4 ± 23·7 10–100	76·8 ± 16·8	83·2 ± 26·1	NS
Bodily pain	78·9 ± 25·6 10–100	67·1 ± 39·7	83·5 ± 24·5	NS
General health perceptions	59·5 ± 18·7 25–100	50·7 ± 12·7	63·4 ± 19·9	NS

NS, not significant.

ing a limited effect on the patient's life. Three patients (27%, 3/11) acknowledged small-to-moderate effect on their life with scores ranging from 4 to 7. All three were female patients, aged 19–45 years and suffering from alopecia areata universalis, that is, the complete loss of hair and body hairs. The DLQI scores were lower for patients with patchy alopecia areata and for male patients (all scored below 4). However, the difference according to gender was not significant.

Regarding the DLQI related to CMC, we obtained 21 answers with a mean score of 0·7 (0–6). The majority of the patients (15/21) scored 0 and therefore had no current QoL impact of chronic candidiasis. Three patients had scores ranging from 2 to 6. However, there was no link between high DLQI and depression or with diminished RAND-36 scores.

Discussion

We report here the first study focused on specific impairment of HQoL related to APECED using three validated self-reported questionnaires in a cohort of Finnish patients. APECED is a rare multiorgan disease belonging to the autoimmune polyglandular syndromes. However, beyond the burden of lifelong daily hormonal replacement therapy for several endocrine disorders (HP, AD, hypothyroidism and diabetes), patients may present several other disabling manifestations such as eye manifestations leading to blindness, disfiguring skin disease (vitiligo, alopecia), reproductive impairment, CMC that impairs everyday life, sexual life (vaginitis in female patients) and potentially leading to lethal oral squamous cell carcinoma. Uncertainty of the disease with possibly new components is an additional source of stress. Lastly, the clinical signs and progression of the disease components may vary in patients, even in the same family. Significant alteration of the QoL may lead to isolation, depression and even suicide.[2,5] To our knowledge, the real burden of APECED patients has never been assessed using validated QoL tools. Only Løvås *et al.* has reported about nine APECED patients with QoL impairment.[14] However, their study was focused on Addison's disease and included mainly patients with primary AD and APS 2. The questionnaire used was the SF-36, and the fatigue questionnaire and working disability were also analysed. Interestingly, these Norwegian APECED patients displayed the lowest scores for general health, vitality and role-physical scores. Other scores were also decreased such as social functioning or role-emotional.[14] In our current and larger series, only age and duration of the disease significantly correlated with fatigue, impaired well-being and general health. We did not find any link between a specific disorder or between the number of accumulated disorders. Not surprisingly, fatigue, vitality, social functioning and general health were also all positively correlated ($P < 0{\cdot}05$). Of note, all the patients with AD received substitution with oral hydrocortisone.

Importantly, we found mild-to-severe depressive symptoms in 29% (8/27) of our patients according to RBDI. Symptoms were however mainly mild in 22% (6/27) and moderate to severe in 7% (2/27). Patients scoring a mild score are usually eligible for short-term psychosocial intervention rather than anti-depressive drugs. Two of them are currently followed and received anti-depressive treatments. Interestingly, two additional patients, who scored 0, are currently under treatment, reflecting most likely its efficacy. However, such a symptom scale is not equivalent to clinical diagnosis of depression. The diagnosis of depression is made during a psychiatric interview, based on evaluation of both intensity and duration of the symptoms (for diagnosis, the symptoms must last over 2 weeks). Thus, we cannot rule out that some of our patients had high scores because of temporary distress with fluctuating symptoms, without a clear depressive syndrome. Compared to available data, the prevalence of depression in Finland was estimated about 5·9% to 6·5% according to

Table 3. Spearman correlation of RAND36

	Age	Duration	Fatigue	Well- being	Social functioning	Physical health	Physical functioning	Bodily pain	General health	Emotion
Age	–	–	$r = 0{\cdot}468$ $P = 0{\cdot}02$	$r = 0{\cdot}474$ $P = 0{\cdot}02$	$r = 0{\cdot}114$ $P = 0{\cdot}58$ NS	$r = 0{\cdot}049$ $P = 0{\cdot}81$ NS	$r = -0{\cdot}260$ $P = 0{\cdot}19$ NS	$r = -0{\cdot}249$ $P = 0{\cdot}23$ NS	$r = 0{\cdot}431$ $P = 0{\cdot}04$	$r = 0{\cdot}328$ $P = 0{\cdot}10$ NS
Duration	–	–	$r = 0{\cdot}48$ $P = 0{\cdot}01$	$r = 0{\cdot}459$ $P = 0{\cdot}02$	$r = 0{\cdot}05$ $P = 0{\cdot}79$ NS	$r = 0{\cdot}06$ $P = 0{\cdot}74$ NS	$r = -0{\cdot}303$ $P = 0{\cdot}132$ NS	$r = -0{\cdot}260$ $P = 0{\cdot}2$ NS	$r = 0{\cdot}450$ $P = 0{\cdot}03$	$r = 0{\cdot}316$ $P = 0{\cdot}11$ NS
Fatigue	$r = 0{\cdot}468$ $P = 0{\cdot}02$	$r = 0{\cdot}48$ $P = 0{\cdot}01$	–	$r = 0{\cdot}757$ $P = 0{\cdot}000012$	$r = 0{\cdot}571$ $P = 0{\cdot}003$	$P = 0{\cdot}003$	$r = -0{\cdot}07$ $P = 0{\cdot}72$ NS	$r = 0{\cdot}121$ $P = 0{\cdot}56$ NS	$r = 0{\cdot}441$ $P = 0{\cdot}03$	$r = 0{\cdot}305$ $P = 0{\cdot}13$ NS
Well-being	$r = 0{\cdot}474$ $P = 0{\cdot}02$	$r = 0{\cdot}459$ $P = 0{\cdot}02$	$r = 0{\cdot}757$ $P = 0{\cdot}000012$	–	$r = 0{\cdot}479$ $P = 0{\cdot}01$	$r = 0{\cdot}486$ $P = 0{\cdot}01$	$r = -0{\cdot}148$ $P = 0{\cdot}48$ NS	$r = -0{\cdot}09$ $P = 0{\cdot}64$ NS	$r = 0{\cdot}584$ $P = 0{\cdot}003$	$r = 0{\cdot}268$ $P = 0{\cdot}19$ NS
Social functioning	$r = 0{\cdot}114$ $P = 0{\cdot}585$ NS	$r = 0{\cdot}05$ $P = 0{\cdot}79$ NS	$r = 0{\cdot}571$ $P = 0{\cdot}003$	$r = 0{\cdot}479$ $P = 0{\cdot}01$	–	$r = 0{\cdot}543$ $P = 0{\cdot}004$	$r = 0{\cdot}163$ $P = 0{\cdot}43$ NS	$r = 0{\cdot}199$ $P = 0{\cdot}34$ NS	$r = 0{\cdot}559$ $P = 0{\cdot}005$	$r = 0{\cdot}206$ $P = 0{\cdot}32$ NS
Physical health	$r = 0{\cdot}049$ $P = 0{\cdot}81$ NS	$r = 0{\cdot}06$ $P = 0{\cdot}74$ NS	$r = 0{\cdot}441$ $P = 0{\cdot}03$	$r = 0{\cdot}486$ $P = 0{\cdot}01$	$r = 0{\cdot}543$ $P = 0{\cdot}005$	–	$r = 0{\cdot}446$ $P = 0{\cdot}02$	$r = 0{\cdot}254$ $P = 0{\cdot}22$ NS	$r = 0{\cdot}406$ $P = 0{\cdot}05$	$r = 0{\cdot}202$ $P = 0{\cdot}32$ NS
Physical functioning	$r = -0{\cdot}260$ $P = 0{\cdot}19$ NS	$r = -0{\cdot}303$ $P = 0{\cdot}132$ NS	$r = -0{\cdot}07$ $P = 0{\cdot}72$ NS	$r = -0{\cdot}148$ $P = 0{\cdot}48$ NS	$r = 0{\cdot}163$ $P = 0{\cdot}43$ NS	$r = 0{\cdot}446$ $P = 0{\cdot}02$	–	$r = -0{\cdot}05$ $P = 0{\cdot}80$ NS	$r = -0{\cdot}02$ $P = 0{\cdot}92$ NS	$r = -0{\cdot}003$ $P = 0{\cdot}98$ NS
Bodily pain	$r = -0{\cdot}249$ $P = 0{\cdot}23$ NS	$r = -0{\cdot}260$ $P = 0{\cdot}2$ NS	$r = 0{\cdot}121$ $P = 0{\cdot}56$ NS	$r = -0{\cdot}09$ $P = 0{\cdot}64$ NS	$r = 0{\cdot}199$ $P = 0{\cdot}34$ NS	$r = 0{\cdot}254$ $P = 0{\cdot}22$ NS	$r = -0{\cdot}05$ $P = 0{\cdot}80$ NS	–	$r = 0{\cdot}104$ $P = 0{\cdot}636$ NS	$r = 0{\cdot}361$ $P = 0{\cdot}07$ NS
General health	$r = 0{\cdot}431$ $P = 0{\cdot}04$	$r = 0{\cdot}450$ $P = 0{\cdot}03$	$r = 0{\cdot}688$ $P = 0{\cdot}0003$	$r = 0{\cdot}584$ $P = 0{\cdot}003$	$r = 0{\cdot}559$ $P = 0{\cdot}005$	$r = 0{\cdot}406$ $P = 0{\cdot}05$	$r = -0{\cdot}02$ $P = 0{\cdot}92$ NS	$r = 0{\cdot}104$ $P = 0{\cdot}636$ NS	–	$r = 0{\cdot}466$ $P = 0{\cdot}02$
Emotion	$r = 0{\cdot}328$ $P = 0{\cdot}10$ NS	$r = 0{\cdot}316$ $P = 0{\cdot}11$ NS	$r = 0{\cdot}305$ $P = 0{\cdot}137$ NS	$r = 0{\cdot}268$ $P = 0{\cdot}19$ NS	$r = 0{\cdot}206$ $P = 0{\cdot}32$ NS	$r = 0{\cdot}202$ $P = 0{\cdot}32$ NS	$r = -0{\cdot}003$ $P = 0{\cdot}98$ NS	$r = 0{\cdot}361$ $P = 0{\cdot}07$ NS	$r = 0{\cdot}466$ $P = 0{\cdot}02$	–

NS, not significant.

the living area (urban or rural) in the ODIN study.[22] The Beck Depression Index (BDI) is slightly different compared to the RBDI questionnaire used here, and the threshold score is above 12 to define possible case of depression. In our series, two patients scored over 12 according RBDI. In 341 Finnish patients with cured well-differentiated thyroid carcinoma, depressive symptoms were reported in the chronic state, that is, 12 years after primary treatment, did not differ from that of a large background population ($n = 6001$), as evaluated by the 15D instrument.[23] Health-related quality of life assessed in a large sample ($n = 6681$) representative of the Finnish population using the same instrument revealed a prevalence of 4·2% for anxiety and 6·5% for depressive disorders.[24] Thus, our results of moderate-to-severe depression in 7% of the patients with APECED are quite similar, albeit slightly higher than in the above-mentioned cohorts. In APECED, however, the origin of the depressive symptoms has not been explored: they could be endogenously related to one of the endocrinopathies, such as AD or hypothyroidism, to the burden of APECED or to some additional factors unrelated to APECED. No statistical association between RBDI score and any of the clinical manifestations was found. Men had slightly more elevated scores than women. However, the scores were within normal ranges, and difference between genders was not significant. Also, Spearman correlation analysis showed a statistically significant association between a low total RBDI and elevated age, as well as long duration of APECED. There was no relation with the age at first onset of APECED or the number of manifestations. Thus, our results suggest that the young adult and teenage patients with APECED could be more fragile when diagnosed with APECED. Young APECED patients have to face, during their youth, the development of successive endocrinopathies, each of them requiring their own treatments and potential complications, disabling CMC and 'disfiguring' dermatoses. On the other hand, with advanced age, patients may get accustomed to their disease and learn little by little to manage their symptoms and live with the disease. However, only longitudinal studies will be able to confirm or not a potential 'improvement' of RBDI scores. Again not surprisingly, there was a negative correlation between fatigue, well-being, social, general health and elevated RBDI scores.

Chronic cutaneous diseases may affect patients deeply,[25] vitiligo especially.[26,27] In our series, only three patients had vitiligo (11%), which is close to the previous Finnish series.[5] The absence of vitiligo effect on QoL can be explained by several reasons: Finnish patients do have a fair skin phototype which make vitiligo less visible and therefore more discrete. Vitiligo may be universal as for one of our patients and therefore not be at all a source of distress. Besides, as our study was performed 30 years after the onset of the disease, it is likely that the patients have got used to vitiligo and are able to cope with it.[26] This is supported by the fact that the 'highest' DLQI score (2) for vitiligo was obtained from the youngest patient, aged 28. Lastly, vitiligo may be minimized by the patients as a minor symptom compared to other disorders that require hormonal treatment. Alopecia areata had an effect on the quality of life in 27% of our patients. Female patients are more affected by hair loss compared to male patients for which alopecia is more easily accepted. It remains hard for women even if the alopecia has been set for years prompting to wear a wig. Despite the absence of statistical significance and nonelevated score, these results should not be neglected in the management of the patient. CMC did not seem to provide elevated scores and therefore impairments. Several explanations can be provided: CMC infection evolves during time and in our experience as in others, infectious episodes tend to be rarer during life of the patients. Besides, patients are often used to self-medicate CMC with local or oral anti-fungal therapies whenever they feel suspicious symptoms of candida infection.

Limitations in our study include mainly the relatively small sample size of patients and the absence of an age-, sex- and dispersed geography-matched Finnish healthy control cohort which would have naturally been valuable in terms of assessing the potential impact of environmental, behavioural and genetic factors on QoL. Genetic factors, however, are not likely to affect our results as the Finnish population is genetically very homogeneous compared to most other populations.[28] Additional factors such as education, occupation, urbanisation and behaviour (e.g. alcoholism) were not analysed. Neither were symptoms of anxiety and/or panic crisis separately explored in our series. We wanted to restrict this study to only three different self-reported questionnaires to improve adhesion. Anxiety is an additional feature that should not be forgotten, though.

We report here one of the largest series of patients, knowing that Finland displays one of the highest incidence of APECED. Besides, as to a control group, it is difficult to obtain a homogenous 'perfect' comparative control group as APECED is peculiar due to the myriad of diseases that may be associated and as symptoms vary according to time. Our questionnaire was self-reported and analysed the answers at a given time in 2012. As pointed out by some patients, the DLQI is based on the past symptoms that occurred the last 7 days. Therefore, the DLQI cannot illustrate the overall lifetime burden of vitiligo, alopecia or CMC. We cannot either completely rule out potential bias due to memory recollection or the wish to stress that disease affected a patient at another period of his/her life, as well as potential external events or seasonal influence that may have played role in the RBDI scores. It is likely that most of the patients learned to live with the disease and coped with it, explaining the rather low rate of impaired scores. Besides, medical management has improved during the past decades and patients with APECED nowadays disclose most likely a better quality of life than in the 1990s.

Concluding remarks

It has been previously shown that APS diseases of type 1 or 2 disclose a stronger burden than the usual 'monoglandular' endocrinopathies.[14] APECED is a complex evolving disease that implies a good knowledge by the physician. Our patients reported sometimes having the feeling to be left alone because of a too complicated disease during which a symptom can be related to various organ dysfunctions and that may leave an

inexperienced physician perplexed. This stresses the necessity of a multidisciplinary approach and the development of national centres of excellence for the management of such rare diseases.

Our results point out that impairment of general health, emotional well-being and vitality is diminished but close to what has been observed previously in a smaller cohort conducted 10 years ago and in a different setting.[14] Even though direct comparison is impossible, the score of our patients appear to be 'better' than those of APS-1 in Norway. We failed to find any link with the number of disorders. The male patients appeared to be more likely to have higher RBDI score suggestive propensity for depression and the young to have a stronger impairment of HQoL.

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