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Infections and demanding endocrine care contribute to increased mortality in patients with APECED

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ABSTRACT

Objective: Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) has variable clinical course. Overall mortality is increased but reasons for this remain largely unknown. Our objective was to assess the causes of death and factors contributing to increased mortality.

Design: A follow-up study of the Finnish APECED cohort in 1970-2019.

Methods: In 34 deceased patients with APECED, causes of death and clinical course preceding the death were analyzed using national registry data, death certificates, autopsy reports, and patient records.

Results: Most common causes leading to death were infections (24%), oral and esophageal malignancies (15%; median age at death 36.7 years; median survival 1.5 years), and diseases of circulatory system (18%). Adrenal crisis was an independent cause of death in two patients. In addition, in four patients, adrenal crisis was a complicating factor during a fatal infection. Other APECED manifestations leading to death were hypoparathyroidism, diabetes, and hepatitis. Other causes of death included accidents (12%), alcohol related causes, and amyotrophic lateral sclerosis. Challenges in the overall, and especially in the endocrine, care contributed to deaths related to carcinomas and adrenal crisis. Age at death and year of death correlated ($r = 0.345$, $P = 0.045$), suggesting improved longevity.

Conclusions: Infections, malignancies and diseases of circulatory system are the most common primary causes of death in patients with APECED. Adrenal crisis is an independent cause of death but more often a contributing factor in fatal infections. Despite the high overall mortality and the demanding care, our results suggest improved patient survival in recent years.

INTRODUCTION

Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal dystrophy (APECED) is a rare disease with mutations in the Autoimmune Regulator (*AIRE*) gene (1). Mutations result in failure of negative selection of thymic autoreactive T cells and impaired function of regulatory T cells (2). APECED is characterized by multiple endocrine and non-endocrine autoimmune manifestations, and clinical course is highly variable. Our recent register-based study showed that Finnish patients with APECED have significantly increased standardized mortality ratios for all-causes and for specific causes such as endocrine and metabolic diseases (3). In the present study, we analyzed more closely the causes of death and circumstances leading to death in order to identify means to improve patient care.

METHODS

All Finnish patients with APECED who were alive from 1970 onwards were included. Altogether 97 patients were assessed; 92 belonged to the original Finnish APECED cohort (4, 5) and five were identified from The Finnish National Care Register for Health Care. Altogether, 34 had died during 1970-2019 (15 females). The study was approved by the Research Ethics Committee of the Hospital District of Helsinki and Uusimaa. Subjects from the APECED cohort had given a written consent.

We collected dates and causes of death from the register maintained by Statistics Finland using Finnish personal identity codes as patient identifiers. We analyzed the clinical course of APECED, the primary cause leading to death, and circumstances preceding death by studying longitudinally collected research data, patient records, death certificates, and autopsy reports. Medical or forensic autopsy report was available for 18/34 patients. The following clinical manifestations were included: chronic mucocutaneous candidiasis (CMC),

hypoparathyroidism (HP), primary adrenal insufficiency (PAI), diabetes, hypogonadism, growth hormone deficiency, hypothyroidism, hepatitis, intestinal dysfunction, exocrine pancreatic insufficiency, nephritis, alopecia, vitiligo, enamel hypoplasia, keratopathy, and rash with fever. The criteria of adrenal crisis were met when two of the following features were combined with impairment of general health: hypotension (systolic blood pressure <100 mmHg), nausea, severe fatigue, fever, somnolence, hyponatremia (<133 mmol/L) or hyperkalemia, and hypoglycemia (6).

Data are presented with medians (range). Pearson's correlation was used for statistical analyses (GraphPad Prism version 8.2.0).

RESULTS

The final study cohort included 34 patients (15 females; 44%). Median age at death was 37.0 years (range, 11.0-69.4) and median number of clinical manifestations was six. Altogether 30 patients (91%) had PAI, and 29 (88%) had HP. Patients were grouped into subgroups according to causes of death: oral or esophageal squamous cell carcinoma (SCC; n=5; 15%), a specific APECED manifestation (n=6; 18%), infection (n=8; 21%), other non-APECED related cause (n=8; 24%), and accidents or alcohol related causes of death (n=7; 21%). Details of these subgroups are presented below. Age at death and year of death correlated positively (r=0.345, P=0.045, Figure 1), suggesting improved survival during recent years.

SCC: Five patients (one female) had deceased at median age of 36.7 years (31.8-50.4), median 1.5 years after diagnosis of malignancy (0.3-10.5). Their median number of disease manifestations was eight (6-10), and all had CMC of oral cavity and/or esophagus with occasional lack of adequate treatment. Two patients were frequent smokers and one had high

alcohol consumption, whereas three patients were non-smokers. Four patients went through resection with curative intention.

Infections: Eight patients deceased at the median age of 24.9 years (13.0-60.3). All had CMC and PAI, and six had HP. Four patients had normal spleen, either in ultrasound during lifetime (n=2) or in autopsy. Infections included three pneumonias, two enteritis, one meningitis, one pericarditis, and one upper respiratory tract infection. Six of the seven patients were hospitalized prior to death, and four of them fulfilled the criteria of adrenal crisis. Detailed clinical information is shown in Table 1.

Deaths due to specific APECED manifestations: Of the six patients, two died at hospital and four died unexpectedly outside health care units at the median age of 47.0 years (11.0-69.4). All these patients had HP, and five had PAI. During hospital care, one died due to fulminant hepatitis at 10.9 years and one due to severe hypercalcemia and acute kidney failure at 69.4 years. Regarding the other four patients, two patients had had hyponatremia, hyperkalemia and low blood pressure levels before death, raising speculations of noncompliance with medications contributing to deaths. One patient presented with persisting low plasma ionized calcium levels, and one patient had had poor therapeutic control of diabetes but no electrolyte imbalance or hypoglycemia before death. No other conditions explaining the death of these patients were found in forensic determination.

Causes of death not associated with APECED: These included ischemic heart disease (n=2), unspecified myocardial degeneration, subarachnoid hemorrhage, cerebral infarction, pulmonary embolism, amyotrophic lateral sclerosis, and aspiration due to obstruction of colon. Diseases of the circulatory system covered 75% of the causes in these eight patients who deceased at the median age of 55.4 years (26.9-62.8). Adrenal crisis and hypocalcemia were excluded in two patients and no information on these findings were available for five patients.

Accidents and alcohol related deaths: Four patients (one female) deceased in accidents and three patients (two females) had an alcohol-related cause of death. Alcohol played a role also in three accidental deaths. No suicide was reported. The median age at death of these seven patients was 42.3 years (13.4-59.4).

DISCUSSION

Our study indicates that oral and esophageal malignancies, infections, and diseases of circulatory system are the most common primary causes of death in patients with APECED. Adrenal crisis is an independent cause of death but more often a contributing factor in fatal infections. Despite the high overall mortality and the demanding care, our results suggest improved patient survival in recent years.

The most common disease-related cause of death was oral and esophageal SCC. Altered T-cell function leading to abnormalities in cytokine-dependent immune responses and CMC probably contribute to increased risk (7-9). All our patients with SCC-related death had severe oral CMC and the use of antifungal drugs was inadequate at least occasionally. These findings highlight the importance of effective treatment and clinical follow-up of CMC, as suggested previously (10), but may also indicate that the current treatment modalities are inadequate.

Adrenal and hypocalcemic crisis have been reported as a major cause of death among patients with APECED (11-13). In our study, two patients who deceased unexpectedly had had signs of inadequate glucocorticoid supplementation before death. Inadequate recognition and treatment of adrenal crisis by physicians have been reported previously (6, 14). We also observed both severe hypocalcemia and hypercalcemia. Increased mortality has been reported in patients with HP but the role of hypocalcemia in the mortality remains unclear (15-17). In

APECED-related HP and PAI, the control of glucocorticoid and calcium homeostasis seems especially challenging, partly due to variable intestinal absorption (18, 19).

We found that infections might be an even more prevalent cause of death than previously reported. The type of infection varied. Two patients deceased of pneumonia, preceded by recurrent pneumonias or severe bronchiectasis and respiratory insufficiency, suggesting autoimmune pneumonitis (20). Adrenal crisis was a contributing factor in 50% of the infections. In fact, infections are one of the main triggers of adrenal crisis and a major cause of death in patients with PAI (21-23). In addition, increased risk for infections is reported in both PAI and HP (17, 24). In APECED, both anti-cytokine autoantibodies and asplenia may increase the risk for severe infections (25, 26). Of our eight patients who died of infections, four had normal spleen while information about the spleen was unavailable for three. Systematic screening for asplenia, adequate vaccinations, and evaluation for antibiotic prophylaxis are important measures to manage the risk of infections. In the recent reports, neutralizing autoantibodies against type I interferons were associated with an increased risk for severe COVID-19 (27, 28). These neutralizing autoantibodies are found in almost all patients with APECED (29). However, further studies are needed to determine the effects of these anti-cytokine autoantibodies.

Diseases that based on present knowledge are not associated with APECED, comprised 24% of the deaths. Diseases of the circulatory system was the most prevalent condition although the etiology was varying. In our previous registry-based study, only two deaths were attributed to cardiovascular disease (3). However, with more detailed data, we determined three additional deaths to be of cardiovascular causes. Cardiovascular diseases have been reported as a major cause of death in patients with adrenal insufficiency, but whether the mortality is increased compared to the general population is not clear (21, 30). Increased mortality and morbidity for

cardiovascular diseases have been reported also in patients with HP (15, 17). There are no previous reports on cardiovascular mortality in patients with APECED.

In summary, the majority of the patients with APECED died for SCC, infections, and diseases of the circulatory system. Our findings suggest that malignancies and adrenal crisis are often preceded by challenges in compliance issues and inadequate or untimely treatment modifications. Experienced multidisciplinary team is needed for effective treatment of all manifestations and complications of the disease. Psychological support should be an integral part of patient management as the disease poses a significant burden to the affected individuals.

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The authors have no conflicts of interest to declare.

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Figure 1. Age at death and year of death of patients divided in five categories depending on the cause of death. Categories include clinical manifestations of APECED, oral and esophageal squamous cell carcinomas (SCC), infections, other causes not related to APECED, and accidents and alcohol related causes. A positive correlation was found between age at death and year of death (r=0.345, P=0.045).

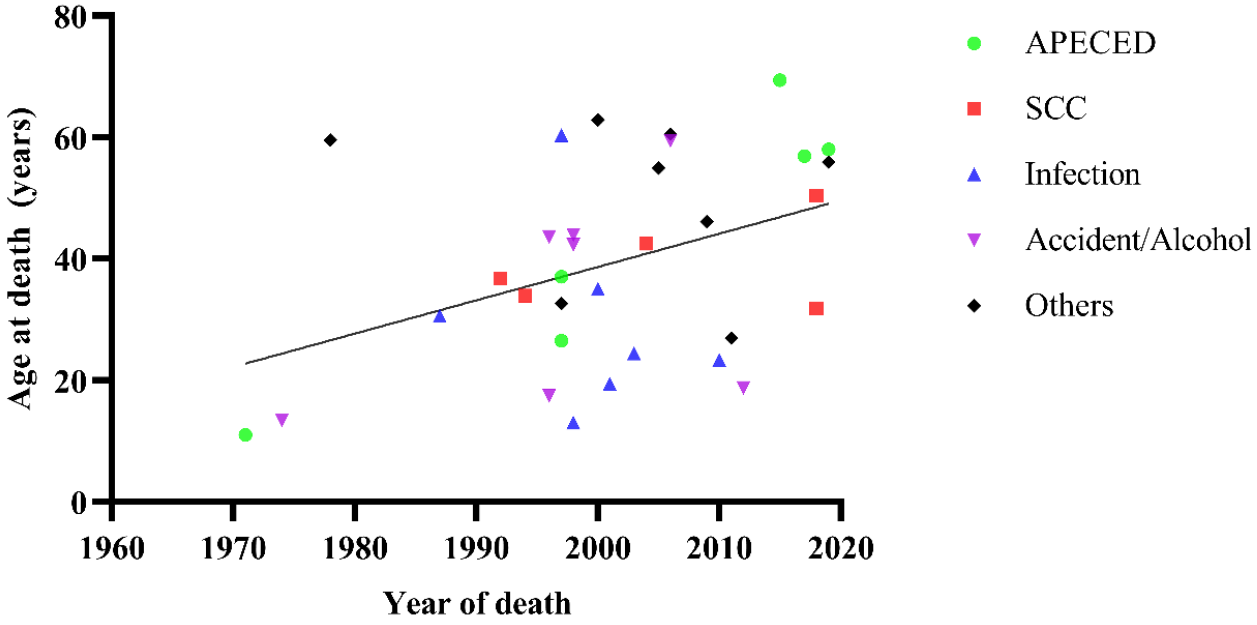

Table 1. Patients with APECED who died for an infection showing age at death (Age), number of clinical APECED manifestations (Components), infection focus (Infection), clinical examinations that were used for the diagnosis, pathogen, hospitalization, intensive care unit (ICU), electrolyte disturbances, hypotension, and adrenal crisis during the death-causing infection. Age is presented in categories to protect patient anonymity.

Age	Components	Infection	Clinical examinations	Pathogen	Hospital /ICU	Asplenia	Electrolytes	Hypotension	Adrenal crisis	Other
11-20	7	Meningitis, septicemia	BC, CSF, CRP 384	*L. monocytogenes*	Y/Y	N	Na↑, K↓	Y	Y	Hepatitis diagnosed recently before death, received methylprednisolone and azathioprine.
11-20	8	Enteritis, septicemia	BC, CRP 129	*C. jejuni*	Y/Y	N	Na↓	Y	Y	Megacolon and ischemia of colon found in autopsy.
21-30	6	Pericarditis	Obduction	*Str. dysgalactiae*	N/N	N	MD	MD	MD	
21-30	8	Pneumonia	X-ray, CRP 68	MD	Y/N	N	N	N	N	Severe bronchiectasis and respiratory insufficiency. Primarily hospitalized due *C. difficile* infection.
21-30	4	URTI	Obduction	MD	Y/N	N	MD	Y	Y	
21-30	8	Enteritis	MD	*C. difficile*	Y/MD	MD	MD	MD	MD	Primarily received antibiotics for urosepsis and later developed *C. difficile* infection.
31-40	6	Pneumonia	Obduction	MD	N/N	MD	MD	MD	MD	
51-60	6	Pneumonia	X-ray, CRP 220	MD	Y/Y	MD	Na↑, K↓	Y	Y	Recurrent pneumonias.

URTI = upper respiratory tract infection; BC = blood culture; CSF = cerebrospinal fluid; CRP = C-reactive protein; X-ray = chest x-ray; L. monocytogenes = Listeria monocytogenes; C. jejuni = Campylobacter jejuni; Str. dysgalactiae = Streptococcus dysgalactiae; C. difficile = Clostridium difficile; MD = missing data; Y=yes; N = no; Na = sodium; K = potassium