European Journal of Endocrinology, 2023, **188**, K17–K23
https://doi.org/10.1093/ejendo/lvad034
Advance access publication 14 March 2023
Brief Report

Pubertal development and hypogonadism in males with autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy: a retrospective study

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Abstract

The aim of this study was to describe the course of puberty and hypogonadism in males with autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (APECED) in a Finnish APECED cohort followed up between 1970 and 2020. Anthropometry, testicular volumes and FSH, LH, and testosterone concentrations were analyzed retrospectively. Forty-three males were followed up until the median age of 42.5 years (range, 16.2-74.8). All subjects fulfilled the clinical criteria for APECED. The median age at the onset of spontaneous puberty was 13.3 years (10.8-14.8). Testosterone medication was used to promote pubertal development from the median age of 14.9 years (13.5-15.7), for 0.7-3.3 years in 8 patients. The median adult height was 173.0 cm and differed from the mid-parental target height on average −1.3 SDS ($P < .001$). Hypogonadism was treated in 6 patients (14%). Azoospermia was found in 3 patients. Further studies are required to explore the role of the autoimmune regulator in sperm production and testicular insufficiency.

Keywords: autoimmune polyendocrine syndrome type 1, gonadal disorders, testosterone, azoospermia

Significance

In this original article, we present data on pubertal development and gonadal function in 43 males with autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (APECED) utilizing unique follow-up data collected over 50 years. Our findings show that the onset and progression of pubertal development were often delayed from average, and several males developed hypogonadism during their lifetime. Many boys required testosterone treatment to induce or promote halted puberty. Most of the patients attained a lower adult height than the mid-parental target height and the average Finnish male height. Our study demonstrates that pubertal development and gonadal function require systematic follow-up as testicular insufficiency and impaired semen quality can be difficult to predict in males with APECED.

Introduction

Autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (APECED), also known as autoimmune polyendocrine syndrome type 1, is an autoimmune disease targeting primarily the endocrine organs. The disease is caused by biallelic mutations in the gene encoding the autoimmune regulator (AIRE) protein.[1-3] Defective AIRE function leads to the release of autoreactive T cells from the thymus into the circulation and to regulatory T-cell deficiency.[4] Affected patients develop autoantibodies against tissue-specific antigens.[4,5]

Over 20 different clinical manifestations of APECED have been described and phenotypes vary greatly.[4,6] Three main manifestations are hypoparathyroidism (HP), primary adrenocortical insufficiency (PAI), and chronic mucocutaneous candidiasis (CMC).[5] In Finnish women with APECED, premature ovarian insufficiency (POI) is the third most common endocrinopathy, affecting almost 70% of female patients.[7] In males with

Received: November 16, 2022. **Revised:** March 6, 2023. **Editorial Decision:** March 8, 2023. **Accepted:** March 10, 2023

APECED, either the pituitary gland or the gonads can be the target organs for an autoimmune process, potentially leading to hypogonadotropic or hypergonadotropic hypogonadism.[6]

Clinical symptoms of male hypogonadism vary by age. In adolescents, hypogonadism disturbs pubertal development and growth, whereas in adulthood, decreased sexual desire, fatigue, and depression are common presentations.[8] In both hypogonadotropic and hypergonadotropic hypogonadism, spermatogenesis is usually impaired.[9] In previous studies on APECED cohorts, the prevalence of testicular failure has varied from 0% to 30% among males.[6,10-13] However, no previous study has described pubertal development, gonadal function, or semen quality in males with APECED in detail.

In this retrospective study, we present data on puberty, growth, and gonadal function in males from a previously described Finnish APECED cohort, with follow-up extending from 1970 to 2020.[6,14]

Methods

Patients

This study is part of the long-term research programme on clinical and molecular characteristics of APECED, carried out at the University of Helsinki, Finland. Ethics approval was obtained from the Research Ethics Committee of the Hospital District of Helsinki and Uusimaa. The study was conducted according to the Declaration of Helsinki. Informed written consent was obtained from all study participants or their guardians (participants aged <18 years). We identified all male patients ($N = 50$) from the previously described Finnish APECED cohort of 95 patients.[6,14] All patients fulfilled the clinical criteria for APECED by having at least 2 manifestations of the classical triad (CMC, HP, PAI). Patient follow-up extended from 1970 to June 2020. For the present retrospective study, 7 patients (17%) were excluded because no data on gonadal function were available ($N = 6$) or the patient deceased before puberty ($N = 1$). Diagnosis of hypogonadism and/or azoospermia was collected from medical records in a total of 43 males. Analysis of pubertal progression included males diagnosed with APECED in prepuberty or early puberty whose records contained information about different stages of pubertal development ($N = 37$).

Clinical data

The data were collected from study files and hospital records. Patients were clinically followed up every 3-6 months in prepuberty and at least yearly during and after puberty. Pubertal development was classified according to Tanner stages[15] based on a clinical evaluation by the attending paediatric endocrinologist responsible for the patient's care. The onset of puberty was defined as Tanner stage 2 for genital development (G2) with testis volumes of ≥4 mL. The onset was considered delayed if G2 and testis volumes ≥4 mL were not attained by age 14.0 years.[16] To evaluate the progression of puberty, we used the puberty nomogram by Lawaetz et al.[17] Testes were measured usually with a ruler but in 8%, with an orchidometer; these methods are equally reliable.[18] The volume of testicles was calculated by the formula: length (cm) × width^2 (cm) × 0.52 = volume (mL).[18] FSH, LH, testosterone, and results of gonadotropin-releasing hormone (GnRH) tests were collected. LH and FSH concentrations reported as ng mL^{-1} were converted to IU L^{-1}: for FSH 1 IU = 0.11388 mg and LH 1 IU = 0.13369 mg.[19] Concentrations were measured with a method available at the time of evaluation at the local university hospital responsible for the patient's care.

When analysing growth and the incidence of APECED manifestations during puberty, we classified G2-3 as early puberty and G4-5 as late puberty. Height was analysed from the end of the prepubertal stage to adult height and compared with the mid-parental target height. The attainment of adult height was defined as growth velocity below 2 cm year^{-1}. Height standard deviation scores (SDSs) were calculated according to Finnish growth references.[20] The age at diagnosis of the following APECED manifestations, if appeared before adult height attainment, were collected: CMC, HP, PAI, diabetes, exocrine pancreatic insufficiency, growth hormone deficiency, hypothyroidism, alopecia, asplenia, atrophic gastritis, bronchiolitis, enamel dysplasia, hepatitis, intestinal dysfunction, keratitis, and vitiligo. In addition, the ages at the time of diagnosis of hypogonadism and azoospermia were determined during the whole study period.

Statistical analysis

Continuous variables were reported as median (range). Mann–Whitney *U*-test was used to compare continuous variables between 2 groups. Paired sample *t*-test was used to analyse the difference between adult height and mid-parental target height. Pairwise deletion was used for missing values. A *P*-value <.05 was considered statistically significant. Statistical analyses were conducted with GraphPad Prism 8 for macOS (version 8.4.3).

Results

Cohort description

Altogether 43 males with APECED were followed until the median age of 42.5 years (range, 16.2-74.8); 3 patients <20 years, and 16 patients had deceased at the median age of 39.7 years (17.4-62.7). The *AIRE* genotype was determined in 36 patients, and 27 of them were homozygous for the Finnish major mutation c.769C > T, p.Arg257Ter. In 8 patients, c.769C > T was compounded with c.967_979del13, p.(Leu323fs) ($N = 4$), c.1638A > T, p.(Ter546Cys) ($N = 2$), or c.891C > A, p.(Asp297Glu) ($N = 2$). One patient had a monoallelic mutation c.967_979del13.

Pubertal development

Data on pubertal development were available for 37 patients. Figure 1 presents the progression of puberty in the puberty nomogram according to genital stages. Altogether, 26 boys did not receive testosterone treatment during puberty and age at G2 was recorded in 21 of them. The remaining 11 boys (11/37, 30%) were treated for delay of puberty or hypogonadotropic hypogonadism during puberty.

In the group that did not receive testosterone, the median age at the onset of spontaneous puberty was 13.3 years (10.8-14.8), and the onset was delayed (≥14.0 years at G2) in 2 of them (2/21, 10%). Testosterone treatment was started for 8 patients (8/37, 22%) to induce ($N = 5$) or to promote halted ($N = 3$) pubertal development at the median age of 14.9 years (13.5-15.7). Testicular volumes were <4 mL in all the subjects who were treated for pubertal induction and ranged from 5.1 to 8.0 mL in subjects with halted pubertal development. The median duration of testosterone treatment was 1.6 years (0.7-3.3). After discontinuation of

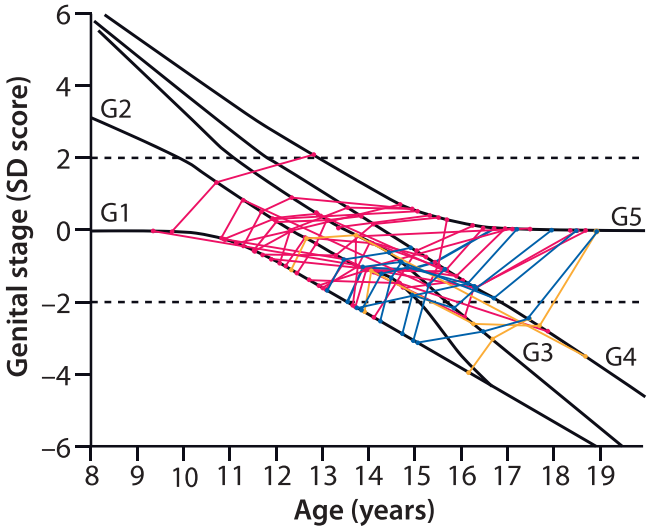

Figure 1. Puberty nomogram presenting the genital stage (SD score) according to age in 37 males with APECED. The black lines indicate the genital stage and the black dashed lines show the normal range of pubertal development. Every patient is marked on the stage line according to age.[17] The red lines represent patients who did not receive testosterone in puberty ($N = 26$), the blue lines represent patients who received testosterone treatment to induce or complete puberty ($N = 8$), and the yellow lines represent patients treated for hypogonadotropichypogonadism in puberty ($N = 3$).

testosterone treatment, pubertal development progressed spontaneously in all 8 patients. In addition to these 8 patients with delayed pubertal development and testosterone treatment, 2 patients were treated for hypogonadotropic hypogonadism at the age of 15.4-15.6 years with testosterone to complete pubertal development. One patient with a constitutional delay of puberty was treated with FSH to promote Sertoli cell proliferation and with testosterone to promote secondary sexual characteristics, and later developed hypergonadotropic hypogonadism (described in detail below).

The median testicular volumes grew steadily from 4.7 mL at G2 to 15 mL at G5 concurrently with increasing testosterone concentrations (Figure S1).

Growth during puberty

For pubertal growth analysis, the study group was divided into 2 subgroups: males with spontaneous puberty ($N = 26$) and males treated with testosterone for induction or maintenance of pubertal development ($N = 8$). Patients diagnosed with hypogonadotropic hypogonadism before attaining adult height were excluded from the growth analyses ($N = 3$). During puberty, there was no significant difference in median height (cm) or weight (kg) in the 2 subgroups, although the height SDS was significantly lower in the patients treated with testosterone (Figure 2). The median height at early puberty was 147.0 cm (−1.6 SDS at the median age of 13.3) in subjects with spontaneous puberty in comparison with 147.2 cm (−2.7 SDS at the median age of 14.5) in patients treated with testosterone. Median adult height did not differ between the 2 subgroups (Figure 2).

In the total cohort of 35 males with APECED, median adult height was 173.0 cm corresponding to −1.3 SDS (range, 144.1-188.8 cm), whereas the median mid-parental target height was 183.8 cm (+0.05 SDS, −0.9 to +1.4, $N = 27$). The

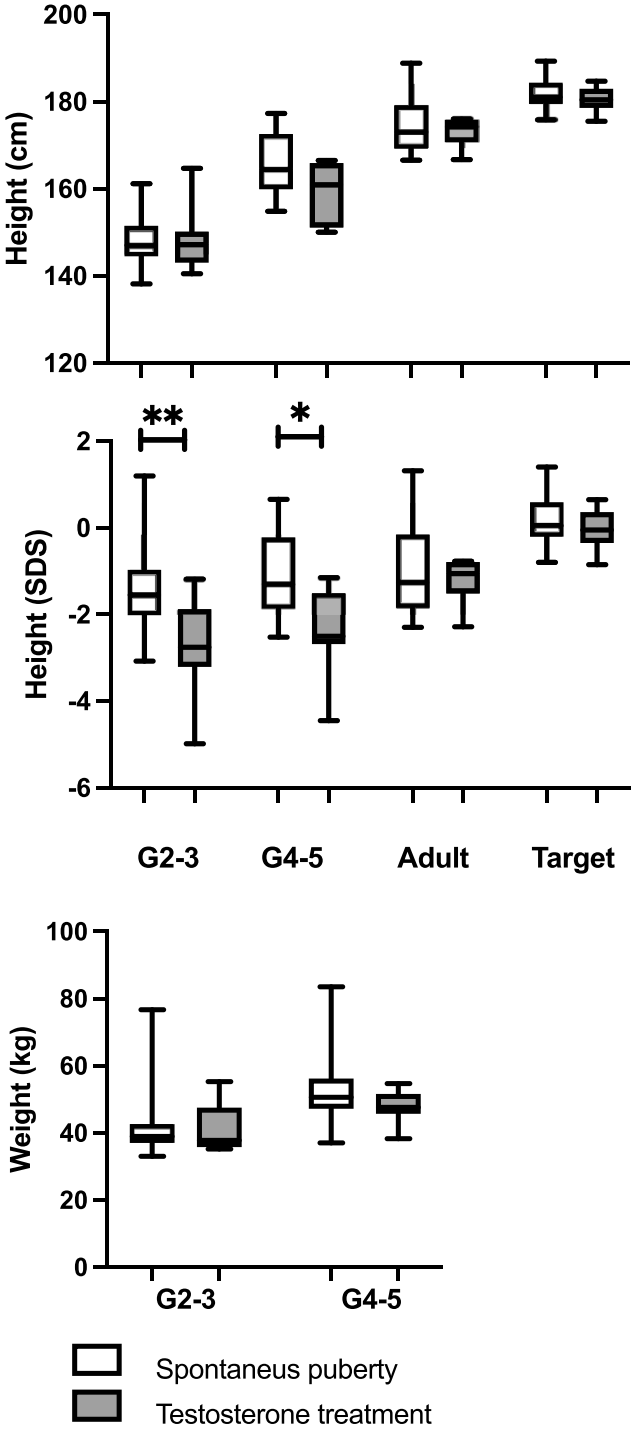

Figure 2. Attainment of height, height SDS, and weight during puberty in 34 males with APECED in relation to mid-parental target height. Cross line indicates the median, box shows the interquartile range, and vertical line shows the range. $*P < .05$; $**P < .01$.

mean difference between adult height SDS and mid-parental target height SDS was −1.3 (95% confidence interval for the difference, −1.9 to −0.7, $P < .001$).

APECED manifestations during puberty

The incidence of APECED manifestations was studied throughout puberty in 37 males (Figure S2). The patients

had 1-8 manifestations when entering puberty (median, 5). During puberty, 1-4 new manifestations developed in 23 patients. Even during late puberty, the manifestations of the classical triad developed: HP, PAI, and CMC. Growth hormone deficiency had been diagnosed in 7 males during prepuberty, and they were treated with growth hormone from the age of 5.4 to 14.2 years until the attainment of adult height or the end of follow-up. Three of them had spontaneous puberty, 2 were treated with testosterone during puberty, and 2 had hypogonadotropic hypogonadism. The adult height SDS differed significantly from the target height in both males with and without growth hormone deficiency ($P = .001$ and .0007, respectively).

Hypogonadism and azoospermia

A detailed description of the patients with hypogonadism and azoospermia is presented in Table 1. Treatment for hypogonadism was initiated in 6 patients (14%, 6/43) at the median age of 20.7 years. In 2 patients, pubertal development was completed with testosterone treatment and their testicular volumes remained small (<2 mL). One patient, treated with FSH and testosterone for constitutional delay of puberty,[21] developed hypergonadotropic hypogonadism after discontinuation of testosterone treatment at 18.9 years. Three adult patients were treated for hypergonadotropic hypogonadism from age 22.4 to 49.5 years.

Seven males had undergone semen analysis. Three had normospermia; 2 of them were homozygous for c.769C > T and in 1, c.769C > T was compounded with c.967_979del13. Azoospermia was found in 2 patients treated for hypogonadism (Table 1). One patient without testosterone deficiency had azoospermia which was confirmed by testicular biopsy presenting Sertoli cell-only syndrome (Table 1, Figure S3).

Fertility

Altogether 10 males (23%, 10/43) had a biological child or children. All these males were homozygous for c.769C > T. One had a delayed spontaneous onset of puberty and 2 had received testosterone treatment to induce or promote pubertal development. Semen samples were analysed in 2/10 males with a biological child with normal findings.

Discussion

This retrospective study describes pubertal development and gonadal function in Finnish males with APECED utilizing unique follow-up data collected over 50 years. The onset of puberty was delayed from average, and several males developed hypogonadism or azoospermia during their lifetime.

Normally, the onset of puberty varies between 9.5 and 13.5 years.[16] Although many males with APECED had pubertal onset delayed from the average,[18,22] puberty progressed within the normal limits (−2 to +2 SDS) in most of them. All males who needed testosterone treatment to promote pubertal development had spontaneous pubertal progression after discontinuation of testosterone treatment. This contrasts with findings in females with APECED, in whom no such spontaneous progression of puberty after the initiation of hormonal replacement therapy for POI has been described.[7] However, fluctuating ovarian function has been reported also in adult women with APECED.[23]

Most of the males with APECED attained an adult height that was below the average height of healthy Finnish males,[20] and also below their mid-parental target height. Lower height SDS during puberty reflected delayed development in patients who received testosterone treatment. There was also no significant difference in weight between the 2 subgroups which could have indicated gastrointestinal problems or excessive glucocorticoid replacement therapy. The reason for the growth deficit remains open, but different APECED components and their treatments might explain it. Growth hormone deficiency was part of the disease in 7 males. The replacement therapy for similar patients has been inadequate before the introduction of recombinant human growth hormone in the 1980s.

In our study, the prevalence of hormonally treated male hypogonadism was increased (6/43, 14%) but lower than previously reported in females (70%).[7] Hypogonadotropic hypogonadism is difficult to differentiate from the constitutional delay of puberty, as seen also in patient 1 who was first treated for hypogonadotropic hypogonadism after which hypergonadotropic hypogonadism became evident. Constitutional delay of puberty may have been the actual cause also in the patients 2 and 3. Pituitary insufficiency as a cause for hypogonadotropic hypogonadism has been reported in only one patient with APECED.[13]

Chronic diseases may impair the regulation of puberty and gonadal function. Our patients had a median of 5 APECED manifestations at puberty onset; this may have contributed to the pubertal delay by altering the central control of pubertal development. In females with APECED, we showed that POI was associated with PAI since 93% of the POI patients also had PAI.[7] In the present study, no association between hypogonadism and PAI was seen in males, which may reflect the immune privilege of the testis or the distinct autoimmune targets in testes compared with ovaries and adrenal cortex.

The blood–testis barrier might have a role in protecting the testes from autoimmune processes, but it protects only meiotic and postmeiotic germ cells, not testosterone producing Leydig cells.[24] The exact aetiology of male hypogonadism in APECED is still unknown, although an autoimmune process is plausible. Testis-specific protein 10 (TSGA10) is needed in spermatogenesis, and autoantibodies against TSGA10 may reflect the development of hypergonadotropic hypogonadism. However, their predictive value for hypergonadotropic hypogonadism is still unclear.[25] Aire$^{-/-}$ male mice generate autoantibodies against sperm, testis, epididymis, prostate gland, and seminal vesicle, associated with lymphocytic infiltration of these structures. Approximately 15% of Aire$^{-/-}$ mice exhibit atrophy of testes and azoospermia; the remaining mice show normal testicular morphology and sperm counts.[26]

Azoospermia was found to be associated with testosterone deficiency and in one subject with normal testosterone concentrations and slightly elevated FSH. It is unclear how the impaired function of AIRE leads to impaired semen quality. It has been suggested that AIRE has a role in the checkpoint for the counterselection of germ cells with mutant genes. *Aire* is expressed sporadically in spermatogonia and spermatocytes in mice.[27] However, the semen quality of males with APECED has not been explored in detail.

The strength of the study was the large patient group that was carefully followed up through their lifetime. However, because of the rarity of APECED, the size of the study group was also a limitation. Also, our study was limited by partly lacking

Table 1. Males with APECED and hypogonadism and/or azoospermia.

	Age at diagnosis (G stage)	*AIRE* genotype	APECED manifestations before hypogonadism	APECED manifestations after hypogonadism	Age at G2 stage	Adult height SDS	The volume of testicles mL before hormonal treatment (age)	Testosterone (nmol L^{-1})	FSH[a] (basal-max IU L^{-1})	LH[a] (basal-max IU L^{-1})	Sperm analysis (age)	Age at the end of the follow-up[b]	Additional information
Hypogonadism in puberty													
Patient 1	14.8 (G2)	c.769C > T/c.967_979del13	CMC, alopecia, vitiligo, exocrine pancreatic insufficiency, enamel hypoplasia, hepatitis, GHD, keratitis, renal tubular acidosis	Diabetes	12.6	−0.8	1.0 (14.8)	MD	0.6-4.2	0.1-1.5		25-30	Constitutional delay of puberty treated as hypogonadotropic hypogonadism. Received testosterone between 14.8 and 17.5 y and FSH between 16 and 17.3 y.
	18.9 (G4)						MD	5.7	12.3	4	Necrozoospermia (19.2). After FSH-LH-hCG-treatment living sperm (20.4)	25-30	Treated for hypergonadotropic hypogonadism with testosterone from the age of 18.9 y.
Patient 2	15.4 (G2)	c.769C > T/c.769C > T	CMC, PAI, hepatitis, exocrine pancreatic insufficiency, GHD, bronchiolitis, hypothyroidism	Diabetes, HP	14.2	−5.9	8.0 (15.2)	0.4	0.5-1.0	0.8-6.7	—	20-25	Treated for hypogonadotropic hypogonadism with testosterone.
Patient 3	15.6 (G1)	c.769C > T/c.769C > T	CMC, HP, PAI, hepatitis, keratitis, enamel dysplasia	Alopecia	MD	−1.0	1.5 (15.6)	MD	1.6-4.8	1.2-2.1	Azoospermia (20)	35-40	Treated for hypogonadotropic hypogonadism with testosterone between 15.6-17.8 and 19.6 y, hCG between 17.8 and 19.6 y.
Hypogonadism in adulthood													
Patient 4	22.4	c.769C > T/c.967_979del13	CMC, HP, PAI, keratitis, enamel dysplasia, alopecia	Diabetes, asplenia	12.3	−2.3	13 (13.5)	MD	14-31	36-228	—	50-55	Hypergonadotropic hypogonadism. Testosterone started because of elevated FSH.
Patient 5	49.5	MD	CMC, HP, PAI	—	MD	−1.4	MD	7.1	16-32	27-222	—	60-65	Hypergonadotropic hypogonadism. Testosterone started due to impotence and low testosterone.
Patient 6	40	c.769C > T/c.769C > T	CMC, HP, keratitis, enamel dysplasia, vitiligo	—	MD	−2.1	34 (33.7)	16	12.5-22.4	21.5-75.1	Azoospermia (35.9)	60-65	Hypergonadotropic hypogonadism. Testosterone started due to high FSH and impotence.
Azoospermia													
Patient 7	16.3	c.769C > T/c.769C > T	CMC, PAI, enamel hypoplasia, keratitis	HP, alopecia, asplenia	13.9	+1.3	9.5 (16.9)	21.0	11.2	5.4	Azoospermia (16.3)	40-45	Biopsy (Figure S3) Later FSH 13.3

Age, testicular volumes, and hormone concentrations at the time of treatment initiation are reported.
Abbreviations: CMC, chronic mucocutaneous candidiasis; G, Tanner stage for genital development; GHD, growth hormone deficiency; HP, hypoparathyroidism; MD, missing data; PAI, primary adrenocortical insufficiency; y, years.
[a]LH and FSH basal and maximum concentrations measured by using GnRH tests.
[b]Age is presented in categories to protect patient anonymity.

retrospective data on pubertal stages. In addition, the reliability of hormonal variables was compromised as the laboratory methods have changed over time.

Our study presents that delayed puberty is common in males with APECED as nearly a third of the patients were treated with testosterone to promote pubertal development. Most of the patients attained lower adult height than the average Finnish male height. In line with earlier observations, this study concludes that the prevalence of hypergonadotropic hypogonadism is lower in males than in females. However, gonadal dysfunction is an important feature of APECED also in males. Pubertal development and gonadal function require systematic follow-up as testicular insufficiency and impaired semen quality can be difficult to predict. The role of AIRE in the mechanisms behind testicular insufficiency should be explored in future studies.

Acknowledgments

The authors acknowledge the work of research nurse Nea Boman.

Supplementary material

Supplementary material is available at *European Journal of Endocrinology* online.

Funding

This work was supported by grants from the Academy of Finland (O.M.); Folkhälsan Research Foundation (O.M.); Helsinki University Hospital (S.L. and O.M.); Novo Nordisk Foundation (O.M.); Paediatric Research Centre, Helsinki University Hospital (S.L.); Päivikki and Sakari Sohlberg Foundation (S.L.); Sigrid Jusélius Foundation (O.M.); The Finnish Foundation for Paediatric Research (S.L.); The Finnish Medical Foundation (M.I.M.).

Conflicts of interest: E.T., E.H., M.I.M., J.T., O.M., and S.L. declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Data availability

Restrictions apply to the availability of data to preserve patient confidentiality. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

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