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Endocrinopathy In Primary Immunodeficiency Patients: A Single Center Retrospective Study

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ABSTRACT

Objective: Inborn errors of immunity (IEI) are a diverse group of inherited diseases that affect the innate and adaptive immune systems, leading to symptoms and signs related to infections, autoimmunity, and allergies. There is a remarkable correlation between IEI and endocrinopathies. Our study aimed to retrospectively analyze the clinical, immunological, and endocrine features of our IEI patient group.

Materials and Methods: We retrospectively reviewed medical records of IEI patients from our clinic.

Results: Our study included 40 patients (23 men, 17 women) with a median age of 37 years (range:24-66). The predominant clinical phenotype observed was primary antibody deficiencies (92.5%). Only two patients had a genetic diagnosis: one with a pathogenic variant in the nuclear factor-kappaB2 deficiency (NFKB2) and another in Wiskott-Aldrich Syndrome (WAS) genes. At diagnosis, only one patient had endocrinopathies, but during the last visit 13 patients (32.5%) developed at least one endocrine pathology, among which thyroid disease was the most common. Thyroid disease was present in 11 patients (four with thyroid nodules, three with primary hypothyroidism, two with primary hypothyroidism and thyroid nodules, one with secondary hypothyroidism, one with Graves' disease). Additionally, adrenal insufficiency was observed in five patients and primary hypoparathyroidism was found in one patient. The patient diagnosed with NFKB2 deficiency was investigated for potential endocrine disorders that could accompany the genetic defect, despite the absence of clinical symptoms. The patient was subsequently diagnosed with central adrenal insufficiency following these investigations. Another patient in our study had primary adrenal insufficiency, primary hypoparathyroidism, thyroid nodule, and chronic mucocutaneous candidiasis. No mutations in the autoimmune regulatory and forkhead box protein P3 genes were detected in the targeted genome sequencing. Further genetic examination was planned for this patient.

Conclusion: In our study, endocrinopathy was a frequent comorbidity observed in our IEI patients. We believe that establishing appropriate screening programs for endocrinopathies in IEI patients is crucial to guiding healthcare professionals.

Keywords: Primary immunodeficiency, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), endocrinopathy, autoimmune thyroiditis

INTRODUCTION

Inborn errors of immunity (IEI), previously known as primary immunodeficiency disorders (PIDs), are inherited disorders and these patients may present with susceptibility to infections or non-infectious complications such as allergy, autoimmunity, autoinflammatory conditions, lymphoproliferative diseases, and malignancy (1). Non-infectious manifestations are also called dysregulation of the immune system. As a result of immune dysregulation in IEIs, autoimmune diseases such as autoimmune cyto-

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penia, enteropathy, endocrinopathies, and arthritis can be observed (2,3). The endocrine system, known as a complex network of glands that regulate body function, is often affected by IEI, and most of these endocrine disorders are hypofunctions that can be treated with supplementation therapy. Early diagnosis and appropriate management are very important for positive long-term outcomes in patients with IEI (4). Two main pathophysiologies are considered for endocrinopathy in people with IEI: the autoimmune response and direct effect of responsible genes (4).

Among the endocrinopathies in the general population, thyroid gland pathologies are the most common. Thyroid hormones are critical determinants of metabolic activity, as well as brain and somatic development in infants and metabolic activity in adults. Thyroid dysfunction is more common in women than in men, and most patients do not exhibit other immunological problems such as systemic autoimmune diseases or immunodeficiencies (5,6). However, autoimmune thyroiditis is also frequently found in IEIs such as common variable immunodeficiency (CVID) and IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked). For this reason, it is recommended that patients with any immune system problems be closely monitored for thyroiditis (7).

Another endocrinopathy that can be encountered in patients with IEI is adrenal insufficiency. Adrenal insufficiency is a rare condition that arises due to insufficient production of adrenal hormones, particularly cortisol, and can be life-threatening when left untreated. Diagnosing adrenal insufficiency can be quite difficult because clinical features are not specific to adrenal insufficiency, and dynamic tests are required for diagnosis (8). Therefore, it is very important to identify patients at high risk for adrenal insufficiency (4).

Multiorgan endocrinopathies associated with IEIs such as IPEX /IPEX-like syndromes and APECED (autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy), have been described. The IPEX syndrome is characterized by immune dysregulation, polyendocrinopathy, and enteropathy, which are due to defects in the function of regulatory T cells (Tregs) caused by a loss of function of the X-linked gene Forkhead box protein P3 (FOXP3). In addition to "classical IPEX", a group of patients with an IPEX-like phenotype, who do not have pathological variants in the FOXP3 gene, have been identified. Many genes, such as interleukin 2 (IL2) receptor alpha (IL2RA- CD25 deficiency), signal transducer and activator of transcription 5b(STAT5b), gain-of-function (GoF) in STAT1/3, lipopolysaccharide responsive beige-like anchor (LRBA), and cytotoxic T-lymphocyte associated protein 4 (CTLA-4) have been implicated in the etiology of this disease. Recently, "Tregopathies" have been proposed to categorize the group of IPEX and IPEX-like diseases characterized by Treg deficiency due to monogenic defects (9). The most common endocrinopathies among patients with IPEX and IPEX-like diseases are type 1 diabetes mellitus and thyroiditis. Additionally, a small number of patients, less than 5%, develop adrenal insufficiency. APECED, also known as autoimmune polyglandular syndrome type 1 (APS-1), is a rare, recessively inherited disorder caused by variants of the autoimmune regulatory gene (AIRE) (4,10). AIRE has an important role in central tolerance induction (11). Impairment of AIRE function leads to autoimmunity in many organs targeted by autoantibodies against organ-specific antigens. In a study of 68 patients examining APECED components, hypoparathyroidism and adrenocortical insufficiency were the two most common findings, affecting 79% and 72% of the patients, respectively. Besides endocrinopathy, patients may also exhibit disease manifestations with varying frequency, such as oral candidiasis, alopecia, vitiligo and keratopathy (12).

Epidemiological studies involving endocrine complications in various types of IEI diseases are limited (13). Our aim was to investigate endocrine dysfunctions in our large and diverse patient cohort with IEI followed at our center and to provide an overview of the pathological background of these dysfunctions.

MATERIAL and METHODS

Study Population

Our retrospective study included patients with IEI (2017-2022), followed at our Immunology and Allergy Diseases Clinic. The patients were diagnosed according to the criteria of the European Society for Immunodeficiencies (ESID) (14). They were classified in accordance with the International Union of Immunology Societies (IUIS) classification (15). Demographic characteristics, laboratory and imaging results, and physical examination information were obtained from the electronic records. Next-generation sequencing was utilized to identify the pathogenic variant in a patient presenting with clinical

manifestations of CVID. Targeted genome sequencing was utilized to identify the pathogenic variant in the patient with primary adrenal insufficiency, primary hypoparathyroidism, thyroid nodule, and chronic mucocutaneous candidiasis. Mutation analysis of exons 1 to 12 of the Wiskott-Aldrich Syndrome (WAS) gene was conducted using the sequencing technique described by Lutskiy et al. (16). Patients with inaccessible information were excluded from the study. The study protocol was approved by our Local Ethics Committee (approval number: İ11-685-22).

Statistical Analysis

Statistical analyses were conducted using IBM® SPSS software version 25. Descriptive statistics were presented as frequency (percent), mean±SD, or median (min-max). The χ^2 test and Fisher's Exact test were used to compare proportions in different categorical groups. Continuous variables were assessed for normal distribution using both visual and analytical methods and analyzed with the Mann-Whitney *U* test or Student`s t-test, as appropriate. An overall type-1 error level was set for inferring statistical significance.

RESULTS

Baseline Characteristics

The median age of the 40 patients (23 men and 17 women) included in the study was 37 years (range 24-66 years). Twenty one (52.5%) patients were employed, 11 (27.5%) were smokers, and 25 (62.5%) had at least one comorbidity. Consanguineous marriage was present in the parents of 15 (37.5%) patients, while 11 (27.5%) had a family history of immunodeficiency. The most common clinical phenotype in our cohort was primary antibody deficiencies (92.5%), and the IEI diagnoses are detailed in Figure 1. According to the information obtained from the patient files, only two patients had a genetic diagnosis: one with pathogenic variant in nuclear factor-kappaB2 deficiency (NFKB2), and the other in WAS genes (exon 2 c.177C > T p.48I missense mutation). The median age of symptom onset was 17.5 years (range 0-48 years), the median age at diagnosis was 27.5 years (range 2-58 years), and the median diagnostic delay was 6.5 years (range 0-33 years). The most common findings at diagnosis included pneumonia (n=30, 75%), upper respiratory tract infec-

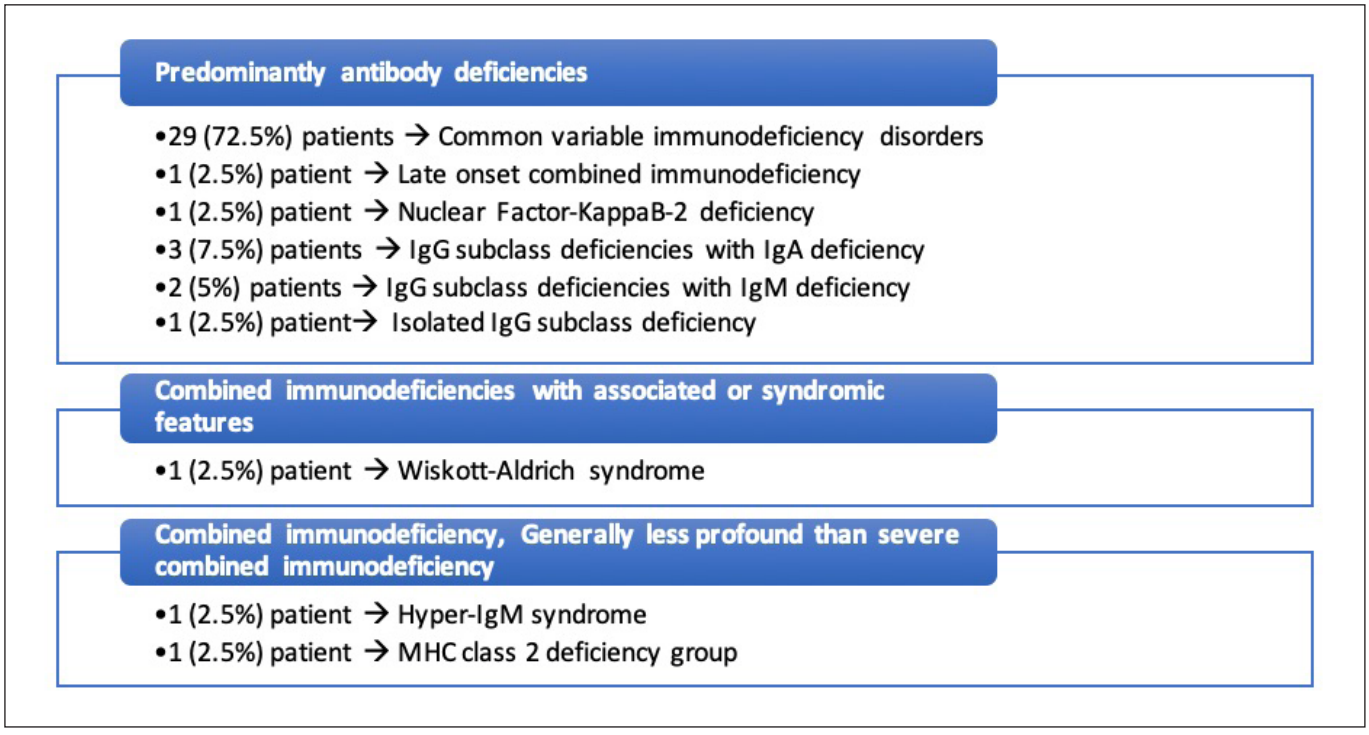

Figure 1. Classification for human inborn errors of immunity (15).
Ig: *Immunoglobulin;* ***MHC:*** *Major histocompatibility complex.*

tion (n=25, 62.5%), and diarrhea (n=8, 20%). Other findings were recurrent otitis media (n=3), recurrent herpes infection (n=3), CMV infection (n=2), bronchitis (n=2), recurrent urinary tract infection (n=2), thrombocytopenia (n=2), and deep neck infection (n=1). Atopy was observed in nine (22.5%) patients and non-endocrinopathy autoimmunity in five (12.5%). Bronchiectasis was present in 20 (50%) patients, gastrointestinal system involvement in 11 (27.5%), hematological involvement in 10 (25%), and malignancy in two (5%). The median immunoglobulin IgG level at diagnosis was 400 mg/dL (range 3-900 mg/dL), IgA was 6.6 mg/dL (range 5-219 mg/dL), and IgM was 27 mg/dL (range 4-775 mg/dL). All patients received IgG replacement therapy (37 intravenous and 3 subcutaneous). Details on lymphocyte counts, peripheral blood lymphocyte subgroups, immunoglobulin levels at the time of diagnosis, and IgG levels under immunoglobulin treatment are provided in Table I.

Table I: Comparison of basic characteristics according to the presence of endocrinopathy.

Characteristics	Overall, n=40	Endocrinopathy		p value
		Yes, n=13	No, n=27	
Male *n (%)*	23 (57.5)	7 (53.8)	16 (59.3)	0.746
Female *n (%)*	17 (42.5)	6 (46.2)	11 (40.7)	
Age*, years	37 (24-66)	34 (24-66)	40 (24-57)	0.754
BMI$^{\epsilon}$, kg/m^2	22.7±4.8	23.7±4.7	22.2±4.8	0.352
Smoking *n (%)*	11 (27.5)	2 (15.4)	9 (33.3)	0.286
Diagnosis of IEI *n (%)*				
CVID	29 (72.5)	8 (61.5)	21 (77.8)	0.451
Others	11 (27.5)	5 (38.5)	6 (22.2)	
Age of symptom onset*, years	17.5 (0-48)	15 (0-48)	18 (0-46)	0.530
Age of diagnosis*, years	27.5 (2-58)	27 (2-58)	28 (8-51)	0.493
Diagnosis delay*, years	6.5 (0-33)	5 (0-27)	7 (0-33)	0.568
Findings in diagnosis *n (%)*				
Pneumonia	30 (75)	10 (76.9)	20 (74.1)	0.845
URTI	25 (62.5)	9 (69.2)	16 (59.3)	0.730
Diarrhea	8 (20)	3 (23.1)	5 (18.5)	0.736
Others	13 (32.5)	3 (23.1)	10 (37)	0.484
Clinical features *n (%)*				
Bronchiectasis	20 (50)	5 (38.5)	15 (55.6)	0.311
GIS involvement	11 (27.5)	3 (23.1)	8 (29.6)	0.664
Hematological involvement	10 (25)	4 (30.8)	6 (22.2)	0.701
Atopy	9 (22.5)	4 (30.8)	5 (18.5)	0.437
Autoimmunity^{+}	5 (12.5)	2 (15.4)	3 (11.1)	0.702
Igs at diagnosis*, mg/dL				
IgG	400 (3-900)	450 (120-640)	390 (3-900)	0.623
IgA	6.6 (5-219)	18 (6.7-219)	6.6 (5-120)	0.177
IgM	27 (4-775)	29 (9-141)	29 (4-775)	0.424
Trough IgG*, mg/dL	780 (230-1360)	720 (230-1360)	800 (500-1320)	0.732
Lymphocytes$^{\epsilon}$, *10^9/L	1957±890.7	2046.9±1036	1914±830	0.664
CD3, %	78±9.1	77.4±9.2	78.3±9.2	0.767
CD4/CD8 ratio	1.3±0.86	1.5±0.88	1.2±0.85	0.313
CD19, %	7.95±4.58	6.46±3.2	8.75±5	0.150
CD16/56, %	12.38±7.31	14.9±8.8	11±6.1	0.121
CD3-HLADR*, %	4 (0-35)	4 (0-23)	5 (2-35)	0.172

BMI: Body mass index, **IEI:** Inborn errors of immunity, **kg:** Kilogram, **m^2:** Square meters, **CVID:** Common variable immunodeficiency, **URTI:** Upper respiratory tract infection, **GIS:** Gastrointestinal system, **Ig:** Immunoglobulin, **mg:** Milligram, **dL:** Deciliter, **L:** Liter, **CD:** Cluster of Differentiation, **HLA:** Human leukocyte antigen, **CD3-HLADR:** Median percentage of HLADR expression from T lymphocytes in flow cytometry. Continuous variables presented with *median (min-max) or $^{\epsilon}$mean±SD or $^{+}$non-endocrinopathy autoimmunity.

Endocrinopathy

While one patient was diagnosed with multiple endocrinopathies (adrenal insufficiency, hypoparathyroidism, and thyroid nodule) at the time of IEI diagnosis, 13 (32.5%) patients had at least one endocrinopathy at the last follow-up. Of these, three (7.5%) had two endocrinopathies, two (5%) had three, and the remaining eight (20%) had one. Thyroid disease was the most common, diagnosed in 11 (27.5%) patients (6 women, 5 men): four (2 women, 2 men) with thyroid nodules, three (3 women) with primary hypothyroidism, two (2 men) with both primary hypothyroidism and thyroid nodules, one (man) with hypothyroidism secondary to pituitary insufficiency, and one (woman) with Graves' disease. In thyroid ultrasonography, five patients had nodules smaller than 1 centimeter, while one had a larger nodule measuring 15*20 millimeters, featuring microcalcification and distinct hypoechoic characteristics. Thyroid fine needle aspiration biopsy was performed on nodules that were large, but since the pathology report indicated atypia of unknown significance and a repeated biopsy yielded the same result, a diagnostic lobectomy was recommended, which the patient declined. Among the five patients with primary hypothyroidism, two tested positive for thyroid autoantibodies (anti-thyroperoxidase antibody (anti-TPO) and anti-thyroglobulin antibody (anti-Tg)), whereas the rest were negative. Additionally, one patient with positive autoantibodies also had Addison's disease. Another patient with hypothyroidism had it secondary to pituitary insufficiency, and one was diagnosed with Graves' disease, confirmed by TSH receptor antibody (TRAb) positivity and diffuse involvement on thyroid scintigraphy. Adrenal disease was present in five (12.5%) patients: two with primary adrenal insufficiency, two with adrenal insufficiency secondary to pituitary insufficiency, and one with a surrenal adenoma. Parathyroid disease was found in two (5%) patients: one with primary hypoparathyroidism and one with secondary hyperparathyroidism. One patient (12.5%) had type 2 diabetes mellitus (Figure 2B). Variables such as gender (p=0.746), age (p=0.754), body mass index (p=0.352), smoking status (p=0.286), diagnosis of CVID (p=0.451), age at first symptom (p=0.53), age at diagnosis (p=0.493), diagnostic delay (p=0.568), common findings at diagnosis (pneumonia p=0.845; upper respiratory tract infection p=0.73; diarrhea, p=0.736), bronchiectasis (p=0.311), gastrointestinal system involvement (p=0.664), hematological involvement (p=0.701), atopy (0.437), and non-endocrinopathy autoimmunity (p=0.702) showed no statistically significant association with the presence of endocrinopathy. Likewise, no significant correlation was observed between endocrine pathologies with IgG, IgA, or IgM levels at diagnosis, lymphocyte count or subsets, or CD3-HLADR expression (Table I).

DISCUSSION

In our cohort of 40 patients with IEI (23 men and 17 women, median age 37 years), 13 patients (32.5%) had at least one endocrinopathy, and five of these patients (12.5%) had multiple endocrinopathies. The diagnoses among patients with multiple endocrinopathies included

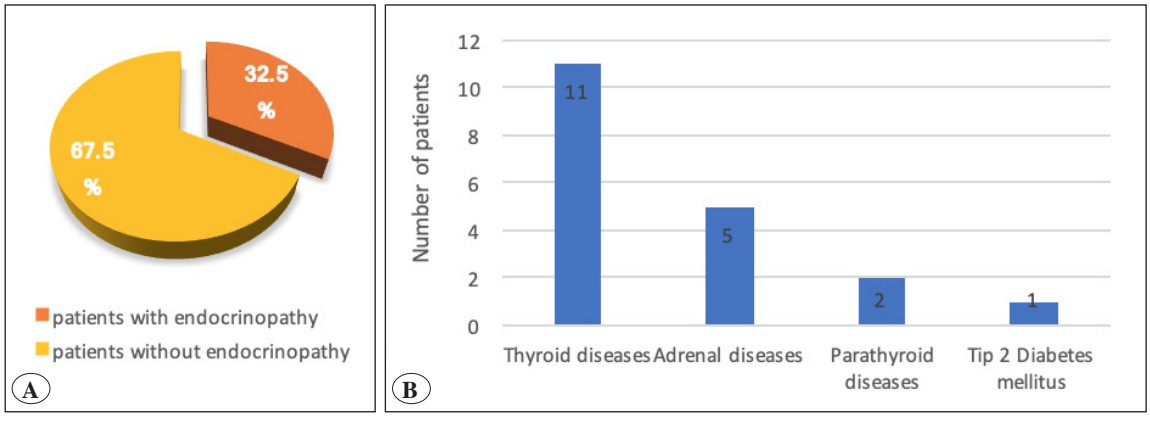

Figure 2. A) Percentage of endocrinopathy, **B)** Frequency of endocrinopathies; thyroid gland pathology in 11(27.5%) patients (n=6 thyroid nodules; n=5 primary hypothyroidism; n=1 hypothyroidism secondary to pituitary insufficiency; n=1 hyperthyroidism); adrenal disease in 5 (12.5) patients (n=2 primary adrenal insufficiency; n=2 adrenal insufficiency secondary to pituitary insufficiency; n=1 surrenal adenoma); parathyroid disease in 2 (2.5%) patients (n=1 primary hypoparathyroidism; n=1 secondary hyperparathyroidism); type 2 diabetes mellitus in one patient

one patient with a thyroid nodule and secondary hypoparathyroidism, one with primary adrenal insufficiency and autoimmune thyroiditis, one with type 2 diabetes mellitus and autoimmune thyroiditis, one with hypoparathyroidism, a thyroid nodule, and primary adrenal insufficiency, and one with hypogonadotropic hypogonadism, secondary hypothyroidism, and secondary adrenal insufficiency. This study presents the characteristics of endocrinopathies observed in our IEI patient cohort.

In our study, the percentage of consanguineous marriages was higher among all IEI patients (37.5%) than in the CVID subgroup (34.5%). While parental consanguinity in our CVID patients was 34.5%, these rates were reported as 5.4%, 12.9%, and 30% in the studies by Oksenhendler et al., Muşabak et al., and Ardeniz et al., respectively (17-19). The rate of consanguineous marriage in our patient cohort was higher than that reported in other studies.

In our study, the most common endocrinopathy we encountered in our IEI patients was thyroid gland pathologies, with 11 (27.5%) patients. Five of these patients had primary hypothyroidism and one had Graves' disease (two patients were anti-TPO positive and one patient were TRAb positive). In a recent study conducted in our country where autoimmune diseases in 92 IEI patients were examined, autoimmune endocrinopathies were observed in 13 (14%) patients and were reported as one of the most common autoimmune comorbidities (20). It was reported that seven of these patients (53.8%) had autoimmune thyroid disease (two patients were anti-TPO positive), five had insulin-dependent diabetes mellitus and one had autoimmune Addison disease. Although the number of patients included in the studies was different, the rates were similar when we compared patients with only primary hypothyroidism and hyperthyroidism within endocrinopathies, respectively (46.1% vs. 53.8%).

Six of our IEI patients with thyroid pathology were women, and five were men. Six (15%) of these patients had thyroid nodules, six (15%) had hypothyroidism, and one had Graves' disease. When we look at the studies on the prevalence of thyroid diseases in the general population; although the prevalence of hypothyroidism varies according to society and diagnostic criteria, it was 0.3% in the 'NHANES III' study and is 5-8 times higher in women than in men; the prevalence of hyperthyroidism (both subclinical and overt) has been reported to be between 0.5% and 1.3%, and it is more common in women (21,22). In a recent meta-analysis on the prevalence of thyroid nodules; the prevalence, regardless of diagnostic techniques, was found to be 24.83% (23). Although our study had a small number of patients, we observed in our IEI patient group that thyroid diseases were more frequent compared to the general population, and the incidence of thyroid diseases did not differ in terms of gender. Additionally, Dalgic et al.'s study findings were similar to our study (20). Our results suggest that IEI diseases may be related to the development of thyroid disease which needs to be confirmed by comprehensive studies including risk analysis.

Adrenal insufficiency was the second most common endocrinopathy in our IEI patients. In our cohort, adrenal gland pathology was present in five (12.5%) patients. Two had adrenal insufficiency secondary to pituitary insufficiency, two had primary adrenal insufficiency, and one had a nonfunctional adrenal adenoma. Among the two patients with central adrenal insufficiency, one had additional pituitary hormone deficiencies (secondary hypothyroidism and hypogonadotropic hypogonadism), while the other exhibited isolated adrenocorticotropic hormone (ACTH) deficiency. Dysfunction of NF-kB transcription factors or regulators, associated with primary immunodeficiency and autoimmunity, has been reported. Loss-of-function variants of NF-kB-2 are known to cause adrenal insufficiency due to isolated ACTH deficiency (4,24,25). Loss of NF-kB-2 function was detected in the genetic analysis of a patient diagnosed with a CVID phenotype, who presented with frequent pneumonia, otitis media, and hearing loss. Upon detecting NF-kB-2 function loss, the patient was screened for additional endocrinopathies. Adrenal insufficiency secondary to isolated ACTH deficiency was diagnosed in this patient, who exhibited nonspecific symptoms such as weakness and fatigue. Treatment with prednisolone at a dose of 5 milligrams twice daily was initiated.

One of the two patients with primary adrenal insufficiency had major histocompatibility complex (MHC) class II deficiency and also had autoimmune hypothyroidism. The other patient presented with concurrent chronic mucocutaneous candidiasis, primary hypoparathyroidism, and a thyroid nodule. The patient with chronic mucocutaneous candidiasis, primary hypoparathyroidism, and primary adrenal insufficiency first exhibited symptoms at age 30, and targeted genome sequencing did not reveal

any mutations in the AIRE and FOXP3 genes. While AIRE is a gene commonly associated with autoimmune adrenal insufficiency and IEI, other genes like CTLA4 and MCM4 (mini chromosome maintenance deficient 4 homolog) have also been implicated in recent studies (11,26,27). Consequently, additional genetic testing was scheduled for the patient.

While endocrinopathy in IEI can result from the direct effects of autoimmune response and responsible genes, it may also arise as a side effect of treatments such as hematopoietic stem cell transplantation (HSCT) (4). In our patient cohort, none had undergone HSCT, and there was no long-term use of corticosteroids, with the exception of those used for treating adrenal insufficiency.

Our study had some limitations. Firstly; since it was a retrospective study, we could not access the average time between the diagnosis of IEI and the diagnosis of endocrinopathy from electronic records. In addition; the small number of patients and the low number of genetic diagnoses in our study are notable limitations; however, it reveals that the incidence of adrenal insufficiency is increased in IEI patients compared to the general population (8). This finding underscores the critical need for diligent assessment of adrenal insufficiency when managing IEI, given its rarity and the serious, life-endangering implications of mismanagement. In addition, we believe that clinicians should question patients diagnosed with adrenal insufficiency in detail in terms of symptoms of IEI in patient groups diagnosed with adrenal insufficiency because some patients in this patient group can be diagnosed with IEI by meticulously questioning the findings that may indicate a cellular immunity disorder.

In conclusion, we have determined that thyroid and adrenal insufficiencies were more prevalent in our IEI patient cohort, compared to the general population. Considering that undiagnosed endocrinopathies can lead to significant morbidity and mortality in patients with IEI, we believe that meticulous monitoring of clinical symptoms related to endocrinopathies and the implementation of effective screening programs, as well as the investigation of patients with multiple endocrinopathies for potential IEI are of paramount importance.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

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