INTERNATIONAL JOURNAL OF COGNITIVE NEUROSCIENCE AND PSYCHOLOGY

HISTORY OF DIAGNOSIS OF TYPE 1 AUTOIMMUNE POLYGLANDULAR SYNDROME AND SPECIFIC FEATURES OF THE COURSE OF THE DISEASE

Saxavayev Davlatbek Arslanbekovich[1], Zubayda Xalbayeva*[2]

[1]Student of the 366th group of the Faculty of Stomatology, Samarkand State Medical University

[2]Assistent, Department of Endocrinologi, Samarkand State Medical University, Samarkand, Republic of Uzbekistan

*Email: zubayda@mail.ru

Abstract: Type 1 autoimmune polyglandular syndrome (APS-1), also referred to as autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (APECED), is an uncommon monogenic disorder presenting with immune-mediated destruction of a variety of endocrine and non-endocrine organs. It was first characterised clinically in the early 20th century and subsequently associated with mutations in the autoimmune regulator (AIRE) gene, which defined its genetic and immunological aetiology. On initial presentation, APS-1 presents most frequently in childhood with chronic mucocutaneous candidiasis, followed by hypoparathyroidism and primary adrenal insufficiency; however, the combination of symptoms varies widely. This article addresses the long journey in which this infection has been known from early clinical characters to molecular diagnosis and describes the unique aspects of its natural history, immunopathogenesis, and chronic phase complications. Knowledge of the time course of diagnostics and the wide range in clinical presentation are very important for early diagnosis, full treatment and a better prognosis. Type 1 autoimune polyglandular syndrome (APS-1) or autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy is an 103 rare genetic disease mainly characterized by immune-mediated destruction of different endocrine organs and chronic mucocutaneous candidiasis. Its diagnostic definition has evolved from a mere clinical recognition of the symptom clusters to molecular identification and characterization of mutations in the autoimmune regulator (AIRE) gene. This article reviews the history of diagnostic methods and emphasizes the unique clinical course of the disease. Particular attention is given to initial presentation of the disease, immunological signs and genetic diagnoses and long-term systemic aspects. Onset is usually in childhood with candidiasis followed by hypoparathyroidism and then adrenal insufficiency, although there is high variability and organ presentation. Immunogenetics and autoantibody profiling have progressed in early diagnosis and risk stratification. Notwithstanding these advances, delayed detection is still common that is related to the rarity and variations in presentation. Awareness of the historical progression of diagnostic approaches and the intricate clinical course is a key to timely treatment, to prevent life-threatening complications and to enhance patient's outcomes.

Keywords: Type 1 Autoimmune Polyglandular Syndrome, APECED, AIRE Gene, Autoimmunity, Hypoparathyroidism, Addison's Disease, Chronic Candidiasis, Endocrine Failure, Monogenic Autoimmune Disorder

Introduction

Autoimmune polyglandular syndrome type 1 constitutes a particular model of genetic autoimmunity. In the past, cases were first reported as a combination of endocrine deficiency along with chronic fungal infections and ectodermal dysplasia. The association of hypoparathyroidism and adrenal insufficiency was first recognized by the clinicians who had little insight on the pathogenetic immunological processes.

In the mid-Twentieth century, the syndrome was defined as a triad comprising of chronic mucocutaneous candidiasis, hypoparathyroidism and primary adrenal insufficiency. The detection of circulating autoantibodies to the endocrine tissues supported the theory of immune destruction. A significant breakthrough came in 1997 when mutations in the AIRE gene on chromosome 21 were found, establishing genetic etiology of APS-1. AIRE is an indispensable mediator of central immune tolerance, inducing expression of tissue-specific antigens in the thymus to facilitate deletion of

autoreactive T cells. Loss of this activity results in multisystem autoimmunity.

On clinical grounds, APS-1 generally presents in early childhood, although the severity and course of the disease signatures can differ greatly. Extraendocrine features including enamel hypoplasia, nail dystrophy, alopecia, keratitis and autoimmune hepatitis may occur before or after the onset of endocrinopathy. This heterogeneity may result in increased time to diagnosis and highlights the clinical roles of history and genetics. Type 1 autoimmune polyglandular syndrome is a monogenic disorder with its genetic pattern being autosomal recessive. It was described in the early 1900s when clinicians saw children with chronic candidiasis, hypocalcemic tetany, and adrenal insufficiency. Diagnosis was based on the classical triad for decades by clinical observation. With the identification of the AIRE gene in the late 1990s, a clearer pathophysiological footing was provided and defective central immune tolerance could be recognized as a driving force for disease.

Lack of thymic negative selection causes autoreactive T cells to persist with subsequent damage to both endocrine and non-endocrine tissues. Apeced syndrome has a wide phenotypic spectrum, which comprises autoimmune thyroiditis, type 1 diabetes mellitus, gonadal failure, pernicious anemia, alopecia, vitiligo and autoimmune hepatitis. Usually, the course is dynamic, with new features being added along the way. Early diagnosis is still difficult, as early signs and symptoms can be nonspecific and isolated. A better knowledge about the historical diagnostic development brings in perspective even modern screening procedures and underlines the relevance of genetic testing, as well as immunological studies among high-risk subjects.

Methodology

Review is derived from retrospective library data, molecular geneticites and immuno-hematologist scientists and clinical cohorts studies published in peer review journal. A literature search of PubMed, Scopus, and Web of Science was performed by using the following key words: “APS-1,” “APECED,” “AIRE mutation,” “autoimmune polyendocrine syndrome type 1,” or/and “clinical progression.

Sources were descriptive early case series, pivotal molecular genetic studies and longitudinal studies of clinical features and outcomes. Information was compiled to describe the time course for development of diagnostic criteria, laboratory tests, and recognition of disease-specific clinical manifestations. Special attention was given to relating the genetic data to phenotypic heterogeneity and course of disease.

Results

Historical perspective indicates that timely diagnosis was based entirely on clinical symptoms, mainly the coexistence of multiple endocrine insufficiencies. Mucocutaneous candidiasis was frequently the initial clinical symptom and occurred in some patients several years before endocrine symptoms. Hypoparathyroidism frequently manifested in early childhood, with tetany and seizures associated with hypocalcemia. Primary adrenal insufficiency usually presented at a later age, with fatigue, hypotension, and hyperpigmentation.

Disease specificity of the autoantibodies allowed for enhanced diagnostic precision by specifying autoimmune etiology before symptomatically evident organ failure. Molecular confirmation by identification of mutations in the AIRE gene is now the gold standard diagnostic test. Diagnosis can be made at the genetic level, before full clinical expression is observed, paving the way for early monitoring.

The disease is characterized by gradual increase in the number of autoimmune symptoms. Patients may also have autoimmune thyroid disease, type 1 diabetes mellitus, hypogonadism, pernicious anemia and chronic hepatitis in addition to the classic triad. Nonendocrine manifestations, including dental enamel hypoplasia and ectodermal dysplasia, are key clinical red flags of MGM. The symptoms and combination of features are so different that even people with the same gene changes may not have them all. Clinical observations from both historical as well as the patient data have been included in our analysis and chronic mucocutaneous candidiasis was seen to be generally the earliest presentation with age of onset occurring predominantly in early childhood. Hypoparathyroidism often develops with hypocalcemia, muscle spasm or seizure. Primary AI is a slow-onset disease but remains an important cause of morbidity and mortality if it goes undetected.

Autoantibody profiling identifies a predominance of antibodies against the type I IFN receptor, IFN-ω

and IFN-α, that can be used as specific immunological markers for APS-1. Organ-specific autoantibodies to parathyroid tissue, adrenal cortex enzymes (21-hydroxylase) and intrinsic factor are often present before clinical presentation. Pathogenic variants of the AIRE gene are identified by genetic testing in most affected individuals.

Longitudinal follow-up reveals that the disorder exhibits an additive pattern, further autoimmune diseases occurring into adolescence and adulthood. Non-endocrine manifestations such as enamel hypoplasia, nail dystrophy, keratopathy, and gastrointestinal symptoms can have a big impact on the quality of life. Pre symptomatic diagnosis is related to better vigilance and less episodes of acute adrenal crisis.

Discussion

The history of APS-1 diagnosis mirrors progress in both immunology and molecular genetics. The first stage recognition by clinical clustering of endocrine failure has been refined with the discovery of distinct auto-antibodies and genetic mutations. The identification of the AIRE gene offered unique insights into mechanisms of central immune tolerance and defined APS-1 as a prototype monogenic autoimmune disease.

Disease is variable with complex interplay between genetic, environmental triggers and immune regulatory factors in dictating disease course. The adventitious order of organ systems affected introduces a challenging aspect to management, and requires lifelong surveillance. Early detection with genetic testing among at-risk families permits anticipatory monitoring for adrenal crisis and other life-threatening complications.

Therapeutic treatment is based on hormone replacement for the endocrine deficiencies and targeted therapy of the autoimmune manifestations. Multidisciplinary management is required because of the multisystemic condition. Immune modulation and gene-targeted treatments are the focus of ongoing studies to determine potential therapeutic options for modifying disease course. The evolution in the diagnosis of APS-1 mirrors events in immunology and molecular genetics. First detected symptomatically, the disease used often to be discovered when life-threatening endocrine failure ensued. Discovery of the AIRE gene transformed and now directs thinking by relating immune tolerance failure to multisystem autoimmunity.

The clinical expression is variable and thus early diagnosis is challenging. A few patients have candidiasis in isolation for many years before endocrine dysfunction becomes apparent and due to this, it is often underdiagnosed. Interferon autoantibodies represent a highly sensitive and specific biomarker that allows suspicion to become aroused earlier, even before full clinical criteria are fulfilled.

It is a slowly progressing and additive autoimmune disease. Severity and age of onset of manifestations can be modified by environmental triggers, modifier genes, and epigenetic effects. Long-term follow-up is needed as second organ involvement may develop decades after the initial presentation. Interdisciplinary therapy endocrinology, immunology, dermatology and gastroenterology system involvement must be integrated.

Although genetic testing has improved, it remains a problem in areas with little access to molecular diagnosis. A high index of suspicion for clinicians is essential to avoid late treatment for adrenal insufficiency and symptomatic hypocalcemia as a leading cause of acute decompensation.

Conclusion

Autoimmune polyglandular syndrome type 1 (APS1) is an infrequent genetic disease with a clear monogenic inheritance as well as variable clinical expressivity. The development of the concept has evolved from clinical observation-thinking to molecular affirmation-based on analysis of the AIRE gene. The condition manifesting initially as chronic candidiasis during childhood evolving into subsequent progressive endocrine failure and other autoimmune presentations. Early diagnosis, genetic analysis and lifelong multidisciplinary follow-up are very important to prevent severe complications and improve long-term outcome. Further exploration of immune tolerance mechanisms may lead to future therapeutic developments for this challenging autoimmune disorder. Type 1 autoimmune polyglandular syndrome: a rare and severe hereditary autoimmune disease with varied clinical presentations. Diagnostic tools have been transformed from identifying characteristic symptom complex to molecular definition by AIRE gene testing and autoantibody workup. This syndrome usually starts

in childhood and gradually involves more endocrine (and non-endocrine) glands. Precocious identification through immunological and gene markers greatly improves control measures and decreases life-threatening complications. Further investigation of the immune tolerance and long-term clinical progression will help in optimizing screening strategies and therapeutic approaches, thus increasing survival and quality of life for those suffering from HPN.

REFERENCES

Ahonen P, Myllärniemi S, Sipilä I, Perheentupa J. Clinical variation of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy. The New England Journal of Medicine.

Nagamine K, et al. Positional cloning of the AIRE gene. Nature Genetics.

Finnish-German APECED Consortium. An autoimmune disease caused by mutations in AIRE. Nature Genetics.

Betterle C, Greggio NA, Volpato M. Clinical review of autoimmune polyglandular syndrome type 1. Journal of Clinical Endocrinology & Metabolism.

Husebye ES, Anderson MS, Kämpe O. Autoimmune polyendocrine syndromes. The New England Journal of Medicine.

Ferre EMN, et al. Redefined clinical features of APECED. Journal of Allergy and Clinical Immunology.

Peterson P, Peltonen L. Autoimmune polyendocrinopathy syndrome type 1 and AIRE. Immunological Reviews.

Perniola R. Twenty years of AIRE research. Clinical Reviews in Allergy & Immunology.

Michels AW, Gottlieb PA. Autoimmune polyglandular syndromes. Nature Reviews Endocrinology.

Oftedal BE, et al. Dominant mutations in AIRE and immune dysregulation. The New England Journal of Medicine.