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ORIGINAL ARTICLE

Is familial screening useful in selective immunoglobulin A deficiency?☆

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Abstract
Introduction: Selective immunoglobulin A deficiency (SIgAD), the most common primary immunodeficiency, is often asymptomatic. High rates of familial clustering have been described in SIgAD, but the causative genetic defect and mechanism of inheritance are unknown.
Objectives: To determine whether familial SIgAD cases show more severe clinical and immunological characteristics than sporadic ones; to investigate the utility of screening first-degree relatives (FDRs) of these patients, and to determine whether symptoms in affected family members are important enough to justify screening.
Patients and methods: Descriptive, cross-sectional study (October 2010–September 2011) of all patients with SIgAD followed up in our centre. Demographic, clinical, and analytical data were reviewed. A familial case was defined as an SIgAD patient with at least 1 affected FDR.
Results: Of the 130 participants, 42 were SIgAD patients and 88 FDR. There were 13 (31%) familial cases and 14 (16%) affected FDRs. Six family members had to be studied in order to detect 1 affected member. There were no clinical differences between familial and sporadic SIgAD cases. The percentages of intestinal disease ($p = 0.001$, OR = 9.57, 95% CI 2.59–35.3), hospitalisations ($p = 0.045$, OR = 4.01; 95% CI 1.10–14.67], and need for chronic treatment ($p = 0.006$, OR = 5.5; 95% CI 1.57–19.54) were higher in affected FDRs than in unaffected ones.
Conclusions: The symptoms were not more severe in familial than sporadic SIgAD cases. Nonetheless, the elevated prevalence of affected FDRs with significant morbidity may justify routine screening of close family members of these patients.

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¿Es útil el cribado familiar en el déficit selectivo de inmunoglobulina A?

Resumen
Introducción: El déficit selectivo de IgA (DSIgA) es la inmunodeficiencia primaria más frecuente, siendo a menudo asintomática. Se ha descrito una elevada agregación familiar, sin conocerse el defecto genético causante ni su mecanismo hereditario.
Objetivos: Definir la utilidad del cribado de los familiares de primer grado de los pacientes con DSIgA valorando si los casos familiares presentan unas características clínicas e inmunológicas más graves que los casos esporádicos (CE) y si los familiares diagnosticados de DSIgA presentan sintomatología clínica significativa para justificar su cribado.
Pacientes y métodos: Estudio transversal descriptivo (octubre del 2010-septiembre del 2011) de todos los pacientes con DSIgA controlados en nuestro centro, con revisión de datos demográficos, clínicos y analíticos. Se consideró como caso familiar (CF) todo aquel con al menos un familiar de primer grado (FPG) con DSIgA.
Resultados: De los 130 participantes, 42 eran pacientes con DSIgA y 88 FPG. Se diagnosticaron 13 CF (31%), 29 CE (69%) y 14 (16%) FPG enfermos (FPG-E). El número necesario a analizar para encontrar un FPG-E fue de 6 familiares. No hubo diferencias clínicas entre los pacientes. Hubo una proporción mayor de patología intestinal (p = 0,001, OR = 9,57, IC del 95%, 2,59–35,3), ingresos (p = 0,045, OR = 4,01; IC del 95%, 1,10–14,67) y necesidad de tratamiento crónico (p = 0,006, OR = 5,5; IC del 95%, 1,57–19,54) en los FPG-E con respecto a los FPG sanos.
Conclusiones: A pesar de no encontrar más complicaciones clínicas en los CF de DSIgA, la elevada prevalencia de familiares afectados con afectación clínica significativa podría justificar la realización sistemática de estos programas de cribado.

Introduction

Selective IgA deficit (SIgAD) belongs to the group of primary immunodeficiencies characterised by a deficit in the production of antibodies. Although SIgAD is the most frequent primary immunodeficiency (PID), its prevalence may vary from 1/163 to 1/18,500 cases, based on the studied population and the definition of SIgAD.[1,2] These variations support a genetic predisposition, and new cases can appear sporadically or be transmitted in a dominant autosomal or recessive manner, or through polygenic inheritance. Thus, a 30% probability of SIgAD has been estimated if there is an affected relative,[3] but no specific genetic defect has been identified, nor has a clear Mendelian inheritance pattern been proven, and expression and penetrance differences persist.[2,4,5] Several genes potentially implicated in its pathogenesis have been identified, suggesting that SIgAD is probably a heterogeneous group of diseases and/or genetic anomalies similar to common variable immunodeficiency (CVID), notably transmembrane activator and calcium modulator (TACI), B-cell activating factor (BAFF-receptor), proliferation-inducing ligand (APRIL), cytotoxic T lymphocyte-associated protein-4-inducible co-stimulator (CTLA4-ICOS) and recombinant activating gene (RAG1), polymorphism, which could be associated a higher risk of presenting SIgAD, coeliac disease, and CVID.[2,4,6–10] In addition to sharing genetic defects, familial aggregation and the known risk of SIgAD progressing to CVID suggest that they are probably part of a wide spectrum of the same disease.[2,11] Furthermore, certain haplotypes HLA (A1, A29, B8, B14, DR3, DQ2) have been associated with a greater risk of SIgAD, although this association is not clear because these haplotypes are also associated with the autoimmune diseases frequently associated with this defect.[2,12–14]

Most patients (85%–90%) affected by SIgAD are asymptomatic. The clinical signs of symptomatic patients are wide ranging, including recurrent sinopulmonary infections, infections and gastrointestinal disorders, allergies, autoimmune processes and neoplasias, with more frequency than the general population.[2,5,15,16]

Although the diagnosis of SIgAD is usually made by analysis of serum immunoglobulins during the evaluation of recurrent respiratory infections, many other cases are diagnosed ''accidentally'', as part of a laboratory evaluation for coeliac disease, allergy, or autoimmune disease.[8]

Prevalence of SIgAD is high among family members, and no studies have as yet been undertaken to compare the clinical and/or immunological difference among familial (FC) and sporadic (SC) cases. As a result, the severity, prognosis and need for complementary tests cannot be assessed. In this context, we set out to evaluate the prevalence of SIgAD in first-degree relatives (FDR) of SIgAD patients, determine whether screening family members is a useful strategy in the clinical management of this pathology, and compare the clinical and immunological characteristics in children diagnosed with sporadical SIgAD with those cases where there is an affected first-degree relative (FDR).