Journal of Autoimmunity 62 (2015) 39–44

Contents lists available at ScienceDirect

Journal of Autoimmunity

journal homepage: www.elsevier.com/locate/jautimm

Marked variability in clinical presentation and outcome of patients with C1q immunodeficiency

Rosanne A. van Schaarenburg [a], Lone Schejbel [b], Lennart Truedsson [c], Rezan Topaloglu [d], Sulaiman M. Al-Mayouf [e], Andrew Riordan [f], Anna Simon [g], Maryam Kallel-Sellami [h], Peter D. Arkwright [i], Anders Åhlin [j], Stefan Hagelberg [j], Susan Nielsen [k], Alexander Shayesteh [l], Adelaida Morales [m], Schuman Tam [n], Ferah Genel [o], Stefan Berg [p], Arnoldus G. Ketel [q], J. Merlijn van den Berg [r], Taco W. Kuijpers [r], Richard F. Olsson [s, t, u], Tom W.J. Huizinga [a], Arjan C. Lankester [v], Leendert A. Trouw [a, *]

[a] Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands
[b] Department of Clinical Immunology, Laboratory of Molecular Medicine, Rigshospitalet, Copenhagen, Denmark
[c] Department of Laboratory Medicine, Section of Microbiology, Immunology and Glycobiology, Lund University, Lund, Sweden
[d] Dept of Pediatric Nephrology and Rheumatology, Hacettepe University Faculty of Medicine, Ankara, Turkey
[e] Pediatric Rheumatology Department, King Faisal Specialist Hospital & Research Center, Alfaisal University, Riyadh, Kingdom of Saudi Arabia
[f] Alder Hey Children's NHS Foundation Trust, Liverpool, United Kingdom
[g] Department of Internal Medicine, Radboud University Medical Center, Nijmegen, The Netherlands
[h] La Rabta Hospital, Tunis, Tunisia
[i] University of Manchester, Manchester, United Kingdom
[j] Department of Clinical Science and Education, Sachs' Children's Hospital, Karolinska Institutet, Stockholm, Sweden
[k] Pediatric Rheumatology Rigshospitalet, Copenhagen, Denmark
[l] Department of Dermatology and Venereology Umeå University, Umeå, Sweden
[m] Nephrology Unit from Hospital Dr Molina Orosa. Ctra. Arrecife-Tinajo, Lanzarote, Spain
[n] Asthma & Allergy Clinic of Marin & San Francisco Inc, San Francisco, USA
[o] Dr Behcet Uz Children's Hospital, Izmir/Konak, Turkey
[p] Pediatric Immunology, The Queen Silvia Children's Hospital, Goteborg, Sweden
[q] Department of Pediatrics, Spaarne Hospital, Hoofddorp, The Netherlands
[r] Emma Children's Hospital, Academic Amsterdam Medical Center (AMC), Dept of Pediatric Hematology, Immunology and Infectious Disease, University of Amsterdam (UvA), Amsterdam, The Netherlands
[s] Centre for Allogeneic Stem Cell Transplantation, Karolinska University Hospital, Sweden
[t] Division of Therapeutic Immunology, Department of Laboratory Medicine, Karolinska Institutet, Sweden
[u] Centre for Clinical Research Sörmland, Uppsala University, Sweden
[v] Department of Pediatrics, Leiden University Medical Center, Leiden, The Netherlands

ARTICLE INFO

Article history:
Received 9 April 2015
Received in revised form
22 May 2015
Accepted 1 June 2015
Available online 26 June 2015

Keywords:
Autoimmunity
C1q deficiency

ABSTRACT

Objective: Globally approximately 60 cases of C1q deficiency have been described with a high prevalence of Systemic Lupus Erythematosus (SLE). So far treatment has been guided by the clinical presentation rather than the underlying C1q deficiency. Recently, it was shown that C1q production can be restored by allogeneic hematopoietic stem cell transplantation. Current literature lacks information on disease progression and quality of life of C1q deficient persons which is of major importance to guide clinicians taking care of patients with this rare disease.

Methods: We performed an international survey, of clinicians treating C1q deficient patients. A high response rate of >70% of the contacted clinicians yielded information on 45 patients with C1q deficiency of which 25 are published.

Abbreviations: CRP, C-reactive protein; FFP, fresh frozen plasma; GI, gastrointestinal infections; HSCT, hematopoietic stem cells transplantations; SLE, systemic lupus erythematosus.

* Corresponding author. Dept. of Rheumatology, C1-R, Leiden University Medical Center, PO Box 9600, 2300 RC Leiden, The Netherlands. Tel.: +31 715265723.
E-mail address: L.A.Trouw@lumc.nl (L.A. Trouw).

http://dx.doi.org/10.1016/j.jaut.2015.06.002

Infections
Systemic lupus erythematosus

Results: Follow-up data of 45 patients from 31 families was obtained for a median of 11 years after diagnosis. Of these patients 36 (80%) suffer from SLE, of which 16 suffer from SLE and infections, 5 (11%) suffer from infections only and 4 (9%) have no symptoms. In total 9 (20%) of the C1q deficient individuals had died. All except for one died before the age of 20 years. Estimated survival times suggest 20% case-fatality before the age of 20, and at least 50% of patients are expected to reach their middle ages.
Conclusion: Here we report the largest phenotypic data set on C1q deficiency to date, revealing high variance; with high mortality but also a subset of patients with an excellent prognosis. Management of C1q deficiency requires a personalized approach.

1. Introduction

C1q deficiency is a rare hereditary disorder, which is strongly associated with development of Systemic Lupus Erythematosus (SLE) [1,2]. The first C1q deficient patient was reported in 1979 [3]. To date more than 60 cases of C1q deficiency have been published with various mutations [4–8]. C1q deficiency has been observed in persons from several ethnic backgrounds [1].

C1q is the recognition molecule of the classical pathway of the complement system and together with C1r and C1s it forms the C1 complex. This complex is important for recognizing e.g. immune complexes and to activate the complement system. C1q is mainly produced by macrophages and immature dendritic cells and has several ligands including bound IgM, complexed IgG but also DNA and CRP [9–11]. In the context of autoimmunity another important ligand for C1q is present on apoptotic and necrotic cells [12–14]. Hence, C1q is important to clear necrotic cells or apoptotic blebs from the circulation as described as the "waste disposal hypothesis" [15]. When the "waste disposal" is disturbed, apoptotic and necrotic material containing autoantigens accumulates resulting in a state that could predispose to development of autoimmunity like in SLE [16]. In addition to a role in the waste disposal process C1q has also been implicated in modulating the adaptive immune response [17–19]. Collectively these data indicate that absence of C1q may not only predispose to infections but also predispose to autoimmunity because of defective clearance of autoantigens and an altered adaptive immune response [20]. In most identified C1q deficient individuals the clinical presentation is towards autoimmunity and the development of SLE, whereas in some individuals the disease mainly presents in the form of recurrent infections e.g. meningitis and in exceptional cases remains largely unnoticed [5,21].

Until now 16 nonsense and missense mutations have been described which are present in 1 of the 3 chains of C1q (chromosomal location: 1p34–1p36.3) [5,22–25]. Mutations causing C1q deficiency are in most cases present in homozygous form and the parents often report a degree of consanguinity [5].

The treatment of C1q deficient patients has until recently mainly been aimed at the symptoms, rather than reversing the underlying C1q deficiency. The exception in the past has been the infusion of fresh frozen plasma containing C1q in a subset of the patients. This treatment has been well tolerated, led to substantial clinical improvements and did not lead to overt induction of anti-C1q antibody formation [23,26]. Based on the observation that C1q levels could be restored by bone marrow transplantation in C1q deficient mice [27,28], now Hematopoietic Stem Cells Transplantations (HSCT) have been performed in two C1q deficient individuals in Sweden and one in the United Kingdom. In all three cases the transplantation led to restoration of circulating C1q levels and an improvement in clinical symptoms [29–31]. During follow-up two patients did well, whereas the other passed away due to intracerebral hemorrage and multi-organ failure. The risk of HSCT related morbidity and mortality has to be weighed against its potential benefits. HSCT related risk is increased in patients with advanced autoimmune disease, or organ damage caused by recurrent infections. Therefore, insight into the natural history of C1q deficiency is crucial to develop a therapeutic algorithm. Most current C1q deficiency literature reports on the identification of new mutations, in young children, but there is no data available on clinical follow up. In this study, we have conducted a survey by contacting clinicians who are currently treating C1q deficient patients.

The aim of this study was to obtain insight into the prognosis of C1q deficient individuals.

2. Methods

2.1. Questionnaire

To study the clinical follow up of C1q deficient individuals, we designed a questionnaire (Table 1). This was sent by email to the corresponding authors of several case- and concise reports as well as to clinicians treating C1q deficient patients. From the 45 individuals, 25 individuals are published in literature and 20 are undescribed.

2.2. Statistical analysis

The data from the completed questionnaires was analyzed using IBM SPSS Statistics Data Editor Version 20. The odds ratios are reported with 95% confidence interval and a p value. P-values <0.05 were considered significant. The differences between the quality of life in living patients and deceased patients were studied using a nonparametric t-test.

3. Results

3.1. Patient cohort

We received completed questionnaires of 45 C1q deficient individuals from 31 different families originating from 14 countries (Table 1). Although most of the cases were from countries in the Middle East, we also observed cases of native Dutch and Swedish origin. No sex bias was found for C1q deficiency (male 49% - female 51%) or for SLE among the C1q deficient patients (male 42% - female 58%) (Table 3). The median time from diagnosis to completion of the questionnaire was 6 years (range:0–34 years). The deficiency for C1q was mostly identified using hemolytic complement assays (CH50). In 60% of the described C1q deficient patients genetic analysis was also performed to identify the mutation associated with the C1q deficiency. Half of the patients have a mutation that