The role of C1q in (auto) immunity

Schaarenburg, R.A. van

Chapter 3

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

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Rosanne A. van Schaarenburg [1], Lone Schejbel [2], Lennart Truedsson [3], Rezan Topaloglu [4], Sulaiman M. Al-Mayouf [5], Andrew Riordan [6], Anna Simon [7], Maryam Kallel-Sellami [8], Peter D. Arkwright [9], Anders Åhlin [10], Stefan Hagelberg [10], Susan Nielsen [11], Alexander Shayesteh [12], Adelaida Morales [13], Schuman Tam [14], Ferah Genel [15], Stefan Berg [16], Arnoldus G. Ketel [17], J. Merlijn van den Berg [18], Taco W. Kuijpers [18], Richard F. Olsson [19], Tom W.J. Huizinga [1], Arjan C. Lankester [20], Leendert A. Trouw [1].

[1] Leiden, The Netherlands. [2] Copenhagen, Denmark. [3] Lund, Sweden. [4] Ankara, Turkey. [5] Riyadh, Kingdom of Saudi Arabia. [6] Liverpool, United Kingdom. [7] Nijmegen, The Netherlands. [8] Tunis, Tunisia. [9] Manchester, United Kingdom. [10] Stockholm, Sweden. [11] Copenhagen, Denmark. [12] Umeå, Sweden. [13] Arrecife-Tinajo, Lanzarote, Spain. [14] San Francisco, USA. [15] Izmir/Konak, Turkey. [16] Goteborg, Sweden. [17] Spaarne Hospital, Hoofddorp, The Netherlands. [18] Amsterdam, The Netherlands. [19] Uppsala University, Sweden. [20] Department of Pediatrics, Leiden, the Netherlands.

Abstract

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 haematopoietic 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.
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.
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.
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.

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 Haematopoietic 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.

Methods

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.

The questionnaire:
• What is the age, gender and country of origin?
• Are the parents consanguineous?
• At which age was the C1q deficiency established?
• Was the C1q deficiency confirmed by genetic tests?
• What was the clinical diagnosis at the moment of establishing C1q deficiency (Infection/SLE/other)?
• What was the age of first symptoms?
• What were the first symptoms (Infection/SLE/other)?
• What treatment options were applied and what was the response?
• Were there any severe infections? Which type?
• What is the frequency of mild infections? Otitis media / Upper respiratory tract infections / Mild GI infections / Unexplained fever above 38°C (never / 1-2 x per year / 3-5 x per year / > 5 times per year)?
• Had there been any other significant clinical problems presentations after diagnosis?
• Has the patient been successfully vaccinated? Has the patient received plasma, and was this successful?
• Was stem cell transplantation considered? Why (not)?
• Is the patient still alive? Yes (current age) No (age of death and cause of death)
• What is your impression of the overall quality of life of the patient (grade from 1-10 with 1 being very poor and 10 being great)
• Please provide information of affected and unaffected relatives.

Table 1. The questionnaire that was sent to all clinicians treating C1q deficient patients

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.

Results

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 has been previously reported in the literature. These mutations are most commonly in the C1qA and C1qC chains.

Country of origin	*Number of patients*
Australia	1
Greenland	3
Iraq	1
Kosovo	1
Netherlands	7
Pakistan	7
Saudia Arabia	9
Spain	1
Sweden	4
Sudan	2
Tunisia	2
Turkey	4
United Kingdom	2
USA	1

Table 2. Overview of the country of origin of patients with C1q deficiency

Onset of disease

The median age at the time of the diagnosis of C1q deficiency was 9 years, but a wide age range from newborn until the sixth decade of life was observed (Figure 1). Most of the C1q deficiencies were identified as part of the routine work up for patients suffering from SLE or from unexplained recurrent infections. In the asymptomatic or less affected C1q deficient family members the diagnosis of C1q deficiency was often made during family screening. At the time of diagnosis 80% of the patients were suffering from SLE, 11% had only experienced recurrent infections and no

SLE while 36% displayed SLE as well as recurrent infections. Cutaneous, discoid lupus was the most common presentation and related symptoms included a malar rash, oral ulcers, recurrent fever and vasculitis. SLE involving the central nervous system was found in one patient. In our series 7% of the individuals, all male, were asymptomatic when C1q deficiency was diagnosed (Table 3). Overall 9 individuals (20%) died, all except for one before the age of 20 years (alive: N= 36, mean 20.0 years ± 11.5 vs deceased: N = 9, mean 12.6 years ±11.7) (Figure 1).

Among C1q deficient siblings one may present with SLE and/or infections, whereas the other is asymptomatic as previously observed in one Maroccan and one Turkish family [1, 25, 32]. In our series, one female from Sweden, one male from the Netherlands, and 4 affected brothers from the United Kingdom, presenting clinically with SLE and/or infections, had a C1q deficient brother that were completely asymptomatic at an age of 8 to 31 years.

C1q deficient individuals	Number of cases	Percentage of cases
Sex M/F	22/23	49/51
Deceased Y/N	9/36	20/80
Deceased Males	3	14
Deceased Females	6	26
Clinical presentation		
SLE Y/N	36/9	80/20
Only SLE	20	44
Only Infections	6	13
Both SLE + Infections	16	36
No symptoms	3	7
Therapy		
FFP given	14	31
HSCT performed	3	7
HSCT considered	10	22

Table 3. Overview of the questionnaires about the C1q deficient individuals

Infectious diseases

The first symptoms of disease reported for most C1q deficient patients were bacterial infections. The most common bacterial infections reported as first symptoms were recurrent otitis, meningitis, gingivostomatitis and urinary tract infection. In our questionnaire we asked the frequency of milder infections per year. We specifically asked for the more common mild infections such as otitis media, upper respiratory tract infections, mild gastrointestinal infections or unexplained fever (Figure 2). In 11 patients (24%) these recurrent infections did not occur at all, whereas in 34

patients (76%) this was a frequent process typically involving multiple sites of infection. From this group thirteen patients had only suffered from mild infections (29%), three patients had only severe infections (7%) and eighteen patients that had both (40%). Patients suffering from severe infections often also suffered more from milder infections (OR: 5.1, 95% CI: 1.2-21.9, p = 0.029).

Severe infections occurred in 47% of the C1q deficient patients with SLE as well as in 53% of the C1q deficient patients without SLE (OR: 1.1, 95% CI: 0.3-4.9, p = 0.881).

All patients had been vaccinated against the regular childhood diseases such as measles, diphtheria, tetanus and poliomyelitis. One patient did receive vaccinations, but no live-attenuated vaccines. Patients with C1q deficiency are vulnerable for infectious diseases and although it would be obvious to provide additional vaccinations, not all individuals received such vaccinations. From the 45 C1q deficient individuals 30 individuals received additional vaccinations. The additional vaccinations of some patients were against Pneumococcus, Meningococcus, Hepatitis B and the seasonal influenza vaccinations [32].

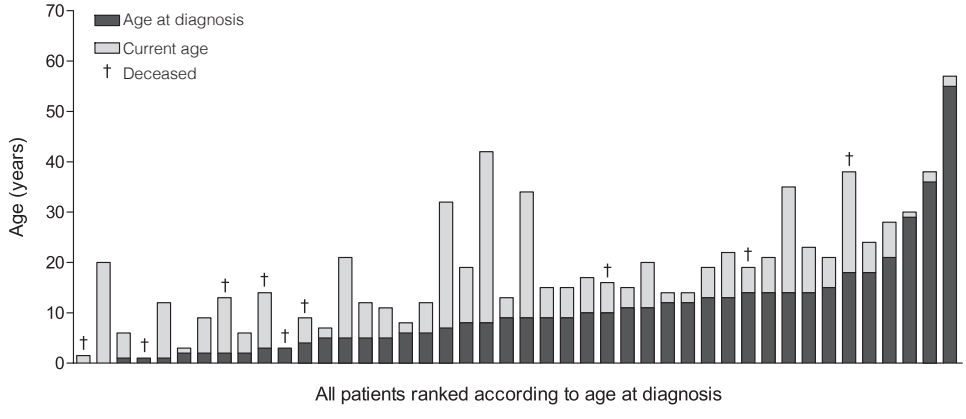

Figure 1. Overview of the age at diagnosis vs. current age (N = 45)

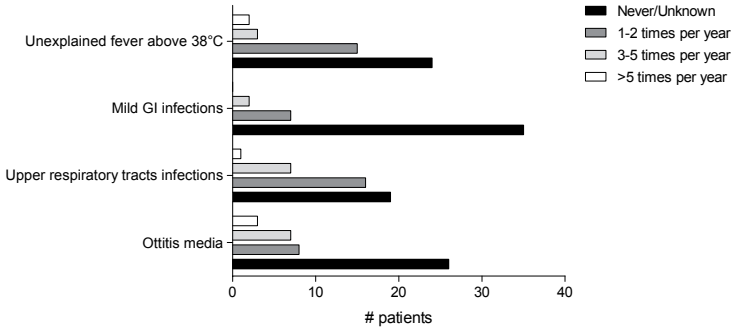

Figure 2. Frequency of 4 milder infections in times per year.

Treatment and outcome

The treatment of C1q deficient patients consisted so far mainly of immunosuppressive therapy such as corticosteroids for SLE or (prophylactic) antibiotic therapy for infections. Other frequently used drugs were chloroquine and hydroxychloroquine as maintenance therapy, while major flares have been treated with rituximab and cyclophosphamide.

The lack of C1q itself has been reversed using fresh frozen plasma (FFP) in 13 out of 45 patients (Table 2). In most patients the FFP is given at weekly intervals, but C1q levels peak early and then decline fast after an infusion [26].

HSCT has been attempted in three C1q deficient patients [29-31]. The allogeneic HSCT has been performed to restore C1q production and mainly treat SLE, but also the immunodeficiency, in C1q deficient children. In all patients the HSCT procedure was successful and normal C1q levels in plasma were obtained. Currently two patients are doing well whereas the other one died of a intracerebral hemorrhage. The latter child was already in a relatively poor condition prior to HSCT. Despite major progress in the field of HSCT, this procedure still has a significant risk profile. From the questionnaire it became clear that several clinicians considered HSCT for their patient but they considered the severity of the clinical symptoms not sufficient to proceed or they reported that no sufficiently matching donor was available to perform HSCT.

In total 9 (20%) patients died during follow-up. The cause of death of 5 C1q deficient patients was septic shock. Other causes of death were bacterial meningitis, gastrointestinal bleeding, Pneumocystis jirovecii pneumonia and cerebral haemorrhage. It is important to note that except for one patient all fatalities occurred in the age group below 20 years (Figure 1). However, the limited follow-up time of the patients in this cohort as a whole does not yet allow strong conclusions.

Estimates of the quality of life

In the questionnaire we asked the treating clinicians to give an estimation of the quality of life of the C1q deficient patient(s). Due to the variability of the clinical presentation of C1q deficiency the estimates of the quality of life varied widely. Remarkably most of the C1q deficient patients are doing well and on a scale from 1-10 (1 very poor – 10 great) the median score was 7 (Figure 3A).

A total of 80% of the C1q deficient patients in this study were still alive with a median age of 19 years and a median quality of life of 7, range (1-10). The 20% of the C1q deficient patients who had died had had a low quality of life (2.44, range (1-6), p = 0.013) and suffered of recurrent infections. In order to have a reference group for the quality of life analyses we asked the clinicians to score also the quality of life of the two SLE patients they most recently examined in their clinic. Also for this group we obtained a median score of 7 (N=7).

The estimated overall survival time (Kaplan-Meier) of the reported C1q deficient patients was evaluated (Figure 3B). In children (less than 20 years old) mortality was estimated to 20%. Moreover, the estimated median survival time seems to be at least 50 years of age although the estimation may not be reliable due to the rather low number of cases.

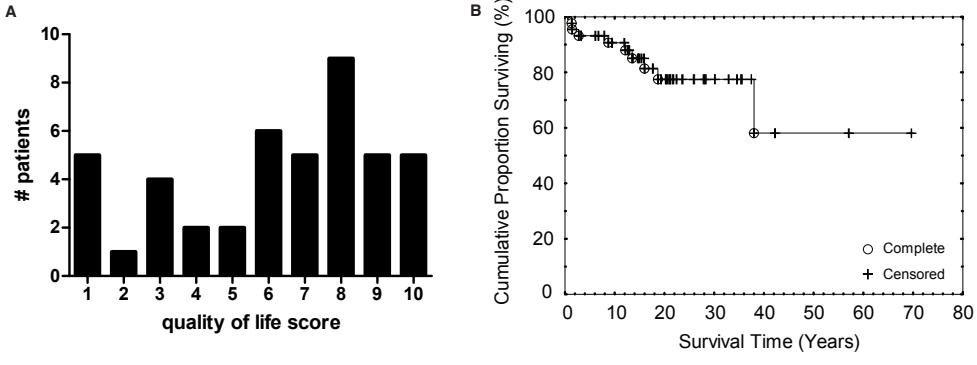

Figure 3. Estimated quality of life and survival analysis.

A. Estimated quality of life, as reported by the treating physicians. The median quality of life is 7.

B. Estimated life expectancy (Kaplan-Meier survival curve) of C1q deficient patients. O = Complete (deceased), + = Censored (at last date of follow up).

Discussion

With this survey we have collected data on the current age, clinical manifestations and quality of life of patients suffering from C1q deficiency. Surprisingly we noticed clear differences. C1q deficiency is associated with a high case-fatality and with early onset of lupus-like disease or full blown SLE in the majority of cases. However, there are also individuals who only suffer from infections without signs of autoimmune disease as well as a sizable group, who are relatively or completely free from symptoms with an excellent quality of life. Until now no data were available on life expectancy and quality of life of individuals with C1q deficiency. It has been described that the course of C1q deficiency is variable [21]. By sending questionnaires to the clinicians who are currently treating C1q deficient patients or have treated deceased patients, we now have a first impression on life expectancy, cause of death, quality of life and treatment regimens. In this study there are some limitations in the use of the questionnaires. We received completed questionnaires covering 45 C1q deficient individuals. Although this is more than 70% of the published cases (as is common for questionnaire based studies [33]), it could reflect a selection bias. Even though this is an international study it may not be a completely worldwide study as C1q deficient individuals in many countries may have been missed. The cases for which we did not receive a response were not restricted to a certain geographical region.

Although C1q deficiency has been reported to occur in many countries around the world we noticed that most patients in this study had their origin from the Middle East, which may reflect to a higher frequency of consanguineous unions in this area [3, 34].

The mutations associated with C1q deficiency include deletions; changes of amino acids or changes in intron-exon splice sites [5, 7, 22]. As most of the mutations result in a condition where no C1q protein is secreted there does not seem to be an obvious relationship between the mutation involved and the clinical outcome of C1q deficiency [4]. Especially since within one family the clinical presentation can vary significantly among individuals homogenous for the same mutation. Differences in phenotype of patients illustrate that other unidentified (epi)-genetic and environmental influences are also important in the overall clinical picture [35, 36]. Understanding what factors determine that some C1q deficient individuals remain asymptomatic whereas others develop SLE, infections or both, will be an important, yet difficult, focus of future studies.

The use of fresh frozen plasma as a treatment option is well described and was applied in 14 patients[23, 26]. In mouse studies bone marrow transplantation in

C1q deficient mice showed positive results and was suggested as a therapeutic option in patients suffering from severe disease [27, 28].

From the questionnaires it became clear that in a substantial number of cases clinicians have considered stem cell transplantation. On the one hand the HSCT should be performed in a patient that is not marked by the underlying SLE or infections, whereas on the other hand performing a HSCT in a patient that is (still) doing fine may not counterbalance the potential risks involved in HSCT. This survey shows that there is a substantial percentage of C1q deficient individuals without any clinical or serological markers of disease. Whether HSCT or gene therapy could be a good option for individuals who have not yet suffered major health problems depends on better insight into the prognosis and on the improvement of these treatments in the future.

Our data show that even during follow up there is enormous diversity in the clinical presentation and severity of symptoms in persons that are deficient for C1q. Even though this case series comprised 45 individuals (comprising the majority of cases known to date) there is no clear algorithm to describe how to manage C1q deficiency. From the data it seems that once the C1q deficient patients reach adulthood that then the chance of fatal infections is reduced. However, follow up data from a longer period is needed to address this question. Remarkably, patients with C1q deficiency showed also other complications. In the questionnaires we received information on two C1q deficient patients who were diagnosed with Moyamoya disease and another patient with signs of Rothmund-Thomson syndrome [24]. The relation between C1q deficiency and to these unexpected complications is not known, but this will likely contribute to a reduction of the life expectancy of these patients.

Conclusion

With this overview we aimed to bring together the currently available information on whether, when and which clinical manifestations occur in C1q deficient patients to be able to make the best possible estimation regarding current treatment options like immunosuppressive drugs, FFP or HSCT. From this survey it became clear that there is enormous diversity in the clinical presentation and severity of symptoms in persons that are deficient for C1q.

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