CEN Case Reports (2020) 9:344–346
https://doi.org/10.1007/s13730-020-00487-5

CASE REPORT

Recurrent macroscopic hematuria in a pediatric patient: is it early to diagnose as having type I hereditary C2 deficiency?

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Received: 14 February 2020 / Accepted: 23 April 2020 / Published online: 5 May 2020

Abstract

Hereditary C2 deficiency is the most common early complement deficiency and characterized by recurrent infections and autoimmunity despite most patients are also asymptomatic. Type I hereditary C2 deficiency is caused by a heterozygous deletion in C2 gene resulting in early stop codon and lack of C2 production. Clinical spectrum may vary and pure nephrological involvement without the presence of recurrent infections is scarce in hereditary C2 deficiency.

We report here a previously healthy 14-year-old boy presenting recurrent self-limited macroscopic hematuria and persistently low serum C4 levels, diagnosed as having type I hereditary C2 deficiency with confirming a novel heterozygote deletion (c.1567 + 22_1567 + 43del) in C2 gene. He has been remained asymptomatic for the next 18 months. Since the diagnosis of C2 deficiency was made in the absence of organ-threatening involvement such as immune complex-mediated glomerulonephritis, we think that early diagnosis and optimal follow-up may improve life-span of the patients with hereditary early complement deficiencies.

Keywords C2 deficiency · C2 gene · Child · Macroscopic hematuria

Introduction

Complement system, as a bridge between innate and adaptive immunity, plays important roles such as opsonization and cleavage of the pathogenic microorganisms, immune complexes and apoptotic cellular debris. The complement system can be activated through three main pathways, including classical complement pathway via C1q, lectin pathway via Mannose-binding lectin (MBL)/ficolin and alternative pathway via factor B, factor D and properdin [1].

Classical complement pathway activation occurs in following order: C1q, C4 and C2, afterwards connects to the common pathway, including C3, C5 and membrane attack complex (C5–9). The hereditary deficiencies of the latter, late complement components are scarce and typically result in recurrent and devastating infections with encapsulated microorganisms, particularly Neisseria spp. Besides, deficiencies early complement components such as C1q, C2 and C4 are more common, however, present with much lesser degree of severe infections but a rising susceptibility to autoimmune disorders [1, 2]. Regarding the genotype, heterozygote pathogenic mutations can be either asymptomatic or present with susceptibility to infections [3]. We have recently reported an adolescent with heterozygote C2

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deficiency who developed encephalitis, necrotizing cutaneous vasculitis and lupus nephritis. This report and the relevant literature suggest that some of the heterozygote C2 mutations may be also linked to autoimmunity [4, 5].

Herein, we describe another pediatric patient with recurrent macroscopic hematuria, yet absence of recurrent infections or autoimmune markers, and diagnosed as having hereditary C2 deficiency thereafter.

Case report

A previously healthy 14-year-old male patient was admitted to our pediatric nephrology department with brown, or cola-colored urine for the last 5 days. His past medical history revealed an upper respiratory tract infection 4 weeks before and one more hematuria episode approximately 1 year ago, which was remitted without medication. Growth indices were in normal range for age and physical examination was totally normal. Vital signs including blood pressure was also normal. Urine microscopy showed 20 red blood cells per high-power field and urine protein/creatinine ratio was 0.12 mg/mg creatinine. Other laboratory studies showed following results: leukocytes: 8300/mm3, neutrophils: 4600/mm3, lymphocytes: 2600/mm3, platelet count: 237000/mm3, hemoglobin: 16 g/dl, blood urea nitrogen: 11 mg/dl, serum creatinine: 0.54 mg/dl, serum albumin: 4.83 g/dl, antistreptolysin O:194 Todd unit C3: 98 (normal range 79–152) mg/dl, C4: 9 (normal range 16–38) mg/dl. Liver enzymes and serum immunoglobulin levels were in normal range for age. Ultrasound imaging of urinary system did not reveal any pathological signs. Echocardiography was normal either. Edema did not appear, and microscopic hematuria resolved in the next 2 days.

He was followed for the next 4 weeks without medication and macroscopic or microscopic hematuria and proteinuria did not recur; therefore, no further interventions were made and the patient has been followed-up for a possible development for a further hematuria attack or proteinuria which would lead confirming an immune complex-mediated glomerulonephritis, particularly IgA nephropathy. For the following 2 months, he suffered from intermittent arthralgia and was referred to the pediatric rheumatology department. Detailed history again did not reveal any pathological signs or symptoms except for recurrent aphthous oral ulcers, occurring one or two times per year. Physical examination did not show arthritis and skin appearance was also normal. We did repeat and elaborated the immunological and rheumatological studies and find out as follows: C3: 127 mg/dl, C4:4 mg/dl, ANA: negative, extractable nuclear antigen (ENA) panel: normal. Due to the normal urine parameters and the lack of positive autoantibodies and signs for autoimmune disorders, including systemic lupus erythematosus, we could not diagnose the patient precisely.

Besides, the permanent low levels of serum C4 in our patient led us to investigate hereditary early complement component deficiencies. Next-generation sequencing disclosed a novel heterozygote deletion (c.1567+22_1567+43del) in C2 gene. Parents could not be evaluated by genetic analysis since they did not give their consents. Mutation tester suggested the mutation as causative with a high possibility. Therefore, we subsequently diagnosed the patient as having autosomal dominant, type I hereditary C2 deficiency, and since there is not an available cure for the disease currently, we have also followed-up him for development of autoimmune disease, particularly SLE for the last 18 months.

Discussion

Hereditary complement C2 deficiency is the most common type of early complement deficiencies over the world. In the view of genotype, two forms of hereditary complement C2 deficiency do exist. Type I complement C2 deficiency means complete lack of C2 related with a heterozygous deletion in C2 gene resulting in early stop codon. Besides, type II complement C2 deficiency is a situation in which biallelic point mutations cause reduced levels of C2. Both type I and II C2 deficiencies were commonly linked to recurrent infections and a broad spectrum of autoimmune manifestations, however, majority of type I deficient patients have been reported as asymptomatic [4, 6]. Besides, symptomatic patients may represent SLE, vasculitis, myasthenia gravis, juvenile idiopathic arthritis and seldomly systemic sclerosis [5, 7]. The prevalence of type 1 hereditary complement C2 deficiency was reported as 7/1000 in northern Caucasian population [8]. Besides, isolated renal involvement is scarce to the best of our knowledge, nonetheless we think that this may be due to underdiagnosing C2 deficiency in clinical practice. We have found two reports of patients with C2 deficiency with biopsy-proven glomerulonephritis [9, 10]. Kim et al. previously showed low serum C2 levels in a 13-year-old patient demonstrating nephrotic-range proteinuria and membranoproliferative glomerulonephritis on renal biopsy. In this ancient report, genetic studies could not been performed [9]. The other patient was reported to have symptoms of nephritic syndrome, including proteinuria, macroscopic hematuria, elevated serum urea, hypoalbuminemia and edema, which appeared at 3 months of age after the vaccination. Renal biopsy confirmed an immune complex-mediated glomerulonephritis and sustained low levels of serum C2 and two mutations in C2 gene, of which one was 28-base pair deletion and the other was a missense mutation yielded the diagnosis of hereditary C2 deficiency [10]. We similarly report here a pediatric patient with sustained low serum C4 levels and recurrent macroscopic hematuria as a pure nephrological manifestation, whose diagnosis of type I hereditary C2 deficiency was confirmed with the presence of a heterozygote deletion in C2 gene.

Persistently low serum C4 level is pathognomonic for hereditary C4 deficiency instead of C2 deficiency, however it can also be a feature of C2 deficiency [11]. The deficient C4 may be due to the activation and consumption of C4 independently from the absence of C2, because it resides before C2 in the cascade [12]. We know that autoantigens or pathogen-derived antigens are opsonized by C1q, C4, C2, and C3 and lead to the formation of immune complexes with the antibodies and thus their clearance via the macrophages. Due to altered tagging of these antigens in hereditary complement deficiencies, immune complex accumulation and precipitation occurs in target organs [13, 14]. Although the exact mechanism of renal involvement in our patient remains doubtful, we think this may be the underlying immunological mechanism. Besides, the asymptomatic period and subtle autoimmune features in our patient, similar to the patients reported in the literature, can also been explained by the lack of frequent severe infections and exaggerated response to the antigens related to responsible pathogens.

The limitations of this report include the lack of determination of functional loss of C2 mutations with serum C2 levels, which could not be available in our country and the lack of information of renal microstructure confirming a diagnosis of IgA nephropathy, which we did not choose to perform, because our patient did not suffer from a new episode of macroscopic hematuria and even did not have low-degree proteinuria.

Nonetheless, by reporting this case, we wish to highlight the unexpected nature of type I hereditary C2 deficiency which may result in a wide spectrum of autoimmune manifestations in the absence of recurrent infections. With overwhelming underdiagnosis, we think that early determination of C2 deficiency in these patients will improve the healthspan by optimizing follow-up, management and prevention of the comorbidities.

Acknowledgements We sincerely thank to our recently passed mentor, Professor Mustafa Yilmaz, who shared his experience on Pediatric Rheumatology with us and encouraged us in academic writing.

Author contributions Dr. Kisla Ekinci, Dr. Balci and Dr. Bisgin conceptualized and designed the report, drafted the initial manuscript, and reviewed and revised the manuscript. Dr. Kisla Ekinci, Dr. Altun, Dr. Altintas and Dr.Atmis followed and investigated the patient, collected data, reviewed and revised the manuscript. The patient was consulted and genetically investigated by Dr. Bisgin. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Funding None.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest regarding all aspects of the paper.

Ethical approval All procedures performed in this case report were in accordance with the ethical standards of the institutional committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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