A CHILD WITH DENSE DEPOSIT DISEASE AND DECREASED CLASSIC COMPLEMENT PATHWAY ACTIVITY

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SUMMARY – We report a rare case of nephritic syndrome underlying dense deposit disease (DDD) with alternative complement pathway dysfunction explained with both C3 nephritic factor (C3NeF) antibodies and DDD associated polymorphism of factor H. An 8-year-old boy presented with macroscopic hematuria, hypertension and periorbital edema followed by persistently low C3 during the 8-week follow-up. Positive C3 staining on immunofluorescence microscopy, supported by dense deposits within the glomerular basement membrane on electron microscopy, confirmed the diagnosis of DDD. Preliminary tests for complement activation showed decreased classic pathway and deficient alternative complement pathway, as well as slightly positive C3NeF, supporting the diagnosis of DDD. Genetic analysis revealed a polymorphism of the complement factor H gene with an increased risk of developing DDD. Supportive therapy led to satisfactory recovery of renal function and normalization of C3. Given the poor prognosis of the disease, proper approach to such specific glomerulopathy is important to avoid or at least slow down progression to end-stage renal disease.

Key words: Dense deposit disease; C3 glomerulopathy; Children; Nephritic syndrome

Introduction

C3 glomerulopathy (C3G) is a rare kidney disease caused by abnormal complement activation consisting of two entities, dense deposit disease (DDD) and C3 glomerulonephritis (C3GN)¹,². Proteinuria, hematuria, acute nephritic/nephrotic syndrome, or even acute renal failure and low C3 levels in a child indicate the possibility of DDD. Complement dysregulation often found in C3G is due to the C3 nephritic factor (C3NeF) antibody directed against alternative pathway C3 convertase leading to uncontrolled complement activation¹. Recent studies point to a certain type of C3G with structurally abnormal complement factor H-related (CFHR) proteins¹. Factor H (CFR) is a plasma glycoprotein that down-regulates complement through preventing assembly and facilitating decay of the alternative pathway C3 convertase, and has a role in the prevention of complement activation¹.

This is a report of a rare and educative case of glomerulopathy with persistently low C3 levels that appeared to be driven by overactivation of the alternative complement pathway in association with both C3NeF antibodies and DDD associated polymorphism of factor H.
Case Report

A healthy 8-year-old boy with a negative family history of kidney disease had a sudden onset of macroscopic hematuria, hypertension and periorbital edema. Laboratory workup showed slightly elevated serum urea (10.7 mmol/L), normal creatinine (87 µmol/L), low serum protein (62 g/L) and albumin (33.4 g/L), as well as proteinuria (1.69 g/24 h; 74.2 mg/m²/h), albuminuria (1096 mg/24 h) and urine casts. The glomerular filtration rate (GFR) measured by Schwartz formula was decreased (80.2 mL/min/1.73 m²). Initial C3 was low (<0.110 g/L), along with normal C4 (0.30 g/L). ASO-titer was slightly elevated (654 UI/mL). Antinuclear antibody (ANA) and anti-neutrophil cytoplasmic antibody (ANCA) were negative, and so were serologic tests for hepatitis C and B. Ultrasound examination showed normal appearance of the kidneys and urinary tract. Diagnostic kidney biopsy was performed after persistently low C3 during the 8-week follow-up. Out of 10/32 glomeruli, segmental or global endocapillary hypercellularity was found alongside mesangial hypercellularity (32/32) (Fig. 1). C3 immunofluorescence was positive (2+) in the mesangium and peripheral capillary loop (Fig. 2). IgG, IgA, IgM, C4, C1q, kappa and lambda staining were negative. Electron microscopy showed dense deposits within the glomerular basement membrane (GBM) (Figs. 3-5). Based on prolonged and diminished serum C3 activity, preliminary tests for complement activation were performed. A reduced total complement activity (alternative pathway) of 3% and total complement activity (classic pathway, hemolytic test) of 43 CH50/mL were found. During treatment, decreased classic pathway and deficient alternative pathway were observed. C3NeF was slightly positive, supporting the
diagnosis of DDD. Genetic analysis found a homozygote for the rare allelic risk factor H, H402, reported as a risk factor for the development of DDD.

**Outcome and follow-up**

The child recovered completely after receiving only supportive therapy (Fig. 6). During the follow-up, he was treated with antihypertensive therapy with strict control of blood pressure and angiotensin-converting enzyme inhibitors to reduce proteinuria. Fluid restriction and specific dietary regimen were applied for 2 weeks, antihypertensive therapy for only one week, and a diuretic (furosemide) was administered only once upon admission to the hospital. Initially, the cause of the disease was thought to be postinfectious glomerulonephritis, so antibiotic treatment was administered for 10 days. C3 and albuminuria returned to normal after approximately 2.5 months. Described therapy led to satisfactory recovery of renal function and normalization of C3. After 4 months, only microscopic hematuria remained. At one-year follow-up, the child still had normal renal function.

**Discussion**

Dense deposit disease, a subtype of C3G, is a rare disease in children with progression towards end-stage renal disease within 10 years of initial diagnosis in about 50% of affected children, with common recurrence after kidney transplantation. Our patient fits well within the previously reported children with this disease. Although in our patient immunofluorescence microscopy was strongly suggestive of C3G, the true nature of the disease was only established by electron microscopy with characteristic dense deposits.

Clinical course and low C3 can also be found in postinfectious glomerulonephritis, but in our case, it was causally associated with DDD. Decreased classic complement pathway and deficient alternative pathway are expected in DDD in accordance with its pathogenesis.

![Fig. 6. Laboratory and treatment follow-up.](image-url)
About 80% of DDD patients, as well as our patient, are positive for C3NeF. We did not find positive C3NeF with partial lipodystrophy, which is often described as an extrarenal manifestation of C3G.

The etiology of DDD has not yet been fully understood. The genetic mutation of complement genes, autoantibodies to complement factor H or B, and autoantibodies that stabilize alternative pathway conversion have already been described. The association of DDD with mutation of CFH gene and factor H-related protein 5 (FHRP5) is well established, but most patients with DDD, as well as our patient, do not have disease-causing mutations in CFH. Our patient had the most common polymorphism of factor H, H402 allele, that is associated with DDD, as well as age-related macular degeneration. The exact mechanism of such a pattern is not known, but it is assumed to be due to the loss of protective binding of factor H to GBM if H402 allele is present. On comparison of the risk H402 allele and protective Y402 allele, consistently greater alternative complement pathway activity is associated with DDD risk alleles. In some cases, streptococcal infection appears to be a trigger for DDD in genetically predisposed individuals, but the exact mechanism is still speculated.

Blood pressure control, minimization of proteinuria, and treatment of dyslipidemia are the recommended strategies of treatment. In case of a more aggressive disease, glucocorticosteroids and mycophenolate mofetil are suggested as a therapeutic strategy. In case of a more aggressive disease, glucocorticosteroids and mycophenolate mofetil are suggested as a therapeutic strategy. In case of a more aggressive disease, glucocorticosteroids and mycophenolate mofetil are suggested as a therapeutic strategy. In case of a more aggressive disease, glucocorticosteroids and mycophenolate mofetil are suggested as a therapeutic strategy. In case of a more aggressive disease, glucocorticosteroids and mycophenolate mofetil are suggested as a therapeutic strategy.

Evidence for a beneficial effect of eculizumab is considered but the response may be related to a specific etiology of the C3 deposits. Plasma exchange should be considered for patients with factor H mutation to provide them with functionally intact factor H. Although the prognosis of children with DDD is still poor, our patient restored kidney function without the need for additional corticosteroid/cytostatic treatment. It takes constant monitoring in order to timely respond to preserve renal function as long as possible. Because the causative mutation was not established, screening of family members for DDD was not performed.

**Conclusion**

We believe that proper diagnosis and individual management of such specific glomerulopathy are important to avoid or at least slow down progression to end-stage renal disease. Therefore, personalized approach to each individual patient should be applied.

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Prikazujemo rijedak slučaj dječaka s nefritičkim sindromom u podlozi bolesti gustih depozita (dense deposit disease, DDD) s disfunkcijom alternativnog puta komplementa koja je objašnjena utvrđenim pozitivnim protutijelima na C3 nefritički faktor (C3NeF) i polimorfizmom gena za faktor H povezanog s DDD. Osmogodišnji dječak prezentirao se makroskopskom hematurijom, hipertenzijom i periorbitalnim edemima s ponavljano niskim vrijednostima C3 tijekom 8 tjedana praćenja. Pozitivno imunofluorescentno bojanje na C3 i negativno na sva ostala protutijela, poduprto gustim depozitima unutar glomerularne bazalne membrane na elektronskoj mikroskopiji, potvrdilo je dijagnozu DDD. Preliminarno ispitivanje aktivacije komplementa pokazalo je ukupnu nedostatnu aktivnost alternativnog puta i smanjenu aktivnost klasičnog puta komplementa, kao i neznatno pozitivan C3NeF, što govori u prilog dijagnozi DDD. Genetska analiza otkrila je polimorfizam gena za faktor H s povećanim rizikom za razvoj DDD. Suportivna terapija dovela je do zadovoljavajućeg oporavka bubrežne funkcije i normalizacije vrijednosti C3. S obzirom na lošu prognozu bolesti važan je pravilan pristup takvoj specifičnoj glomerulopatiji kako bi se odgodila progresija u završni stadij bubrežne bolesti.

Ključne riječi: Bolest gustih depozita; C3 glomerulopatija; Djeca; Nefritički sindrom