Association of Blood Group Antigen CD59 with Disease

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Keywords

CD59 · Blood group · Deficiency · Disease

Abstract

In 2014, the membrane-bound protein CD59 became a blood group antigen. CD59 has been known for decades as an inhibitor of the complement system, located on erythrocytes and on many other cell types. In paroxysmal nocturnal haemoglobinuria (PNH), a stem cell clone with acquired deficiency to express GPI-anchored molecules, including the complement inhibitor CD59, causes severe and life-threatening disease. The lack of CD59, which is the only membrane-bound inhibitor of the membrane attack complex, contributes a major part of the intravascular haemolysis observed in PNH patients. This crucial effect of CD59 in PNH disease prompted studies to investigate its role in other diseases. In this review, the role of CD59 in inflammation, rheumatic disease, and age-related macular degeneration is investigated. Further, the pivotal role of CD59 in PNH and congenital CD59 deficiency is reviewed.

Introduction

A heritable molecule on the membrane of erythrocytes becomes a blood group antigen as soon as a person, who does not carry the identical molecule or the molecule at all, produces antibodies against (epitopes of) the said molecule. Transfusion medicine focuses on the difficulties in serological diagnostics and on provision of compatible erythrocyte units, but for most of these molecules, being a blood group antigen is only a side job. They have major functions in erythrocyte physiology by acting as transporter proteins (e.g., RH [1], JK [2], CO [3], LAN [4], JR [5]), receptors for mediators (e.g., FY [6]), enzymes (e.g., KEL [7], YT [8]), or adhesion molecules (e.g., LU [9]). Variation or deficiency of a blood group antigen can cause erythrocyte malfunction or disease. Causing systemic disease is likely when a blood group antigen is not restricted to erythrocytes but is also present on other cells and tissues. The blood group antigen CD59 blocks the completion of the membrane attack complex on host cells and protects them from unwanted and uncontrolled lysis by the complement system [10]. It is the only membrane-bound inhibitor of the terminal pathway of the complement system; no other molecule providing a backup function exists. CD59 protein variants with impaired function have not been described so far [11–15]. Low density of membrane-anchored CD59 was thought to generate unprotected areas on the cell membrane, which expose the cells or tissues to complement-mediated damage, a concept that has been deduced from paroxysmal nocturnal haemoglobinuria (PNH) where the lack of CD59 on PNH cells causes disease [16, 17]. Published knowledge on the role of CD59 in disease will be investigated in the following.

The Blood Group System CD59

In the blood sample of a 2-year-old girl suffering from a severe neurological disease which was accompanied by recurrent haemolytic episodes, an antibody was found re-
acting with all reagent cells [18]. The patient had been transfused previously, which made the presence of an immune antibody possible, but the specificity of this antibody could not be identified. It took several months until the diagnosis “congenital CD59 deficiency” gave the important clue, and in the year 2012, targeted serological investigation confirmed the presence of an antibody with the specificity “anti-CD59.”

The Working Party Red Cell Immunogenetics and Blood Group Terminology of the International Society of Blood Transfusion (ISBT) defines an erythrocyte antigen as a blood group antigen if a subject has made an antibody directed against this antigen [19]. A blood group system is defined as 1 or more blood group antigens governed by 1 gene or several closely linked genes [19]. In 2014, the membrane protein CD59 was acknowledged as a new blood group system. The system received the number 035, and it comprises 1 antigen so far, which was denoted CD59.1 [20].

### CD59 Gene and Protein

The CD59 gene (HGNC: 1689; Entrez Gene: 966; LRG_41) is located on chromosome 11p13. Several sequences had been deposited at the National Center for Biological Information database; the ISBT acknowledged sequence NG_008057.1 as a reference sequence for CD59. The gene comprises 6 exons which are all present in the transcript variant 1 (NM_203330.2). Additional transcript variants combining different exons are deposited in the database, but all include exons 4, 5, and 6, which contain the coding sequence [21]. The mRNA is translated into a pre-proprotein consisting of 128 amino acids. During the processing of the pre-proprotein to the final, membrane-bound protein, 25 amino acids are cleaved from the amino terminus, and 28 amino acids from the carboxy terminus are cleaved when the glycosylphosphatidylinositol (GPI) anchor is generated [22].

### CD59 Alleles and Phaenotypes

The girl with the CD59 deficiency was homozygous for the deletion of a cytosine at position c.146, which caused a shift of the reading frame and introduced a pre-terminal stop codon (Table 1). Flow cytometry confirmed the lack of CD59 on erythrocytes and leucocytes [12]. Additional genetic variants causing CD59 deficiency were reported (Table 1). Some of these variants carry a premature stop codon, other variants cause a single amino acid substitution. The changes in the CD59 protein introduced by these single amino acid substitutions were crucial for the expression of the protein because all the patients were tested negative for CD59 and were severely ill. The lack of CD59 expression

| ISBT variant No. | Genetic variant | dbSNP numbers | Effect on protein | Expression of CD59 | Test used | Reference |
|------------------|----------------|---------------|------------------|--------------------|-----------|-----------|
| CD59*01N.01 | c.146delA | rs587777149 | p.Asp49Valfs*31 | Erythrocytes: no Granulocytes: no | FCM | [12] |
| CD59*01N.02 | c.123delC, c.361delG | n.a. | p.Val42Serfs*38 | Erythrocytes: no Fibroblasts: no | FCM | [25] |
| CD59*01N.03 | c.266G>A | rs397514767 | p.Cys89Tyr | Erythrocytes and mononuclear cells: no | FCM | [108, 109] |
| CD59.01N.04 | c.146A>T | n.a. | p.Asp49Val | Erythrocytes: no (Cell type not given: no) | FCM | [13] |
| Not yet registered | c.323C>A | rs749308157 | p.Ser108Ter | Lymphocytes: no | FCM | [14] |
| Not yet registered | c.85T>G | rs1564972905 | p.Tyr29Asp | Erythrocytes: <1% Lymphocytes, granulocytes, platelets: no | FCM | [15] |
| CD59*01.02prov. | c.238 A>G | n.a. | p.Arg80Gly | Erythrocytes: yes Normal density | FCM | [24] |

ISBT, International Society of Blood Transfusion; dbSNP, database of Short Genetic Variations; FCM, flow cytometry; IHCS, immunohistochemical staining; n.a., not available. † National Center for Biotechnology Information (NCBI) mRNA reference sequence used for naming the genetic variant is NM_203330.2. ‡ NCBI protein reference sequence used for naming the amino acid variation is NP_976075.1.

ISBT variant No. | Genetic variant | dbSNP numbers | Effect on protein | Expression of CD59 | Test used | Reference |
|------------------|----------------|---------------|------------------|--------------------|-----------|-----------|
| CD59*01N.01 | c.146delA | rs587777149 | p.Asp49Valfs*31 | Erythrocytes: no Granulocytes: no | FCM | [12] |
| CD59*01N.02 | c.123delC, c.361delG | n.a. | p.Val42Serfs*38 | Erythrocytes: no Fibroblasts: no | FCM | [25] |
| CD59*01N.03 | c.266G>A | rs397514767 | p.Cys89Tyr | Erythrocytes and mononuclear cells: no | FCM | [108, 109] |
| CD59.01N.04 | c.146A>T | n.a. | p.Asp49Val | Erythrocytes: no (Cell type not given: no) | FCM | [13] |
| Not yet registered | c.323C>A | rs749308157 | p.Ser108Ter | Lymphocytes: no | FCM | [14] |
| Not yet registered | c.85T>G | rs1564972905 | p.Tyr29Asp | Erythrocytes: <1% Lymphocytes, granulocytes, platelets: no | FCM | [15] |
| CD59*01.02prov. | c.238 A>G | n.a. | p.Arg80Gly | Erythrocytes: yes Normal density | FCM | [24] |
**Fig. 1.** A simplified depiction of the activation pathways of the complement system. C1–C9 denote the complement components 1–9, B denotes complement factor B, C3H2O denotes the hydrolysed form of C3. The letter “b” indicates an activated component or factor. Fat arrows indicate the enzymatic cleavage of a component or factor. The cleaved parts of the complement components (e.g., C3a) are not shown for reasons of simplicity.
was confirmed for the variants c.146delA (p.Asp49Valfs*31), c.123delC (p.Val42Serfs*38), c.266G>A (p.Cys89Tyr), and c.146A>T (p.Asp49Val) in transfection studies [23]. Four alleles were acknowledged by the ISBT as null alleles [20]. In a healthy propositus, the single nucleotide variation c.238A>G (p.Arg80Gly) was detected in heterozygosity [24]. This variant also caused an amino acid exchange which, in contrast, did neither impair the expression of the variant CD59 protein, nor did it impair the cognate epitope recognition by the fluorescent-labelled anti-CD59 antibodies used in flow cytometry. The erythrocytes of this propositus showed the same CD59 density as controls homozygous for the wild-type allele [24]. In contrast, propositi heterozygous for the null alleles c.146delA [18] or c.123delC [25] showed markedly decreased expression of CD59. No data on functionality of this CD59 protein variant are available.

**Activation and Inhibition of the Complement System**

**Pathways of Complement Activation**

The complement system can be activated by 3 pathways which all lead to the assembling of the membrane attack complex (MAC). Antibodies bound to their cognate antigen can activate C1, the first component of the complement system (Fig. 1). Activated C1 activates the components C4 and C2, which form the bimolecular complex C4bC2b, which functions as a C3 convertase (classical pathway of complement activation). The mannose-binding lectin (MBL) recognizes mannose and certain other sugars, arranged in a special pattern (reviewed in [26]). Binding to the recognition patterns activates MBL, which now can activate C4 and C2 to form the C3 convertase of the lectin pathway, which is identical to the classical pathway convertase. The C3 convertases initiated by these pathways convert a large number of C3 molecules into C3b. C3b by complement factors I and H. All these inhibitors and cofactors downregulate complement activation at the level of C3 convertase or C5 convertase. The membrane-bound protein CD59 inhibits the formation of the MAC. CD59 inclines towards the assembling of the C5-C8 and C5-C9 complexes, binds to C8 and C9 [34] and interferes with the polymerisation of the C9 molecules. Thereby, CD59 prevents the assembly of the MAC. CD59 is the only membrane-bound inhibitor that blocks MAC assembly.

**Tissue Distribution of CD59**

CD59 being the only inhibitor of the MAC implies that all kinds of cells and tissues, which come into contact with the complement system, express CD59. CD59 was detected by flow cytometry, immunohistochemistry, or immunocytochemistry on numerous cell types (Table 2). Best known is the presence of CD59 on erythrocytes and leukocytes, but CD59 was also found on platelets [35] and dendritic cells [36]. Cells of the central and peripheral nervous system express CD59, including brain parenchyma [37], neurons [38–40], choroid plexus epithelium [37, 39], ependymal cells [41], Schwann cells [41, 42], and retinal pigment epithelium (RPE) [43, 44]. CD59 is present on the endothelium of arteries, veins, and capillaries [41, 45–47], glomerular endothelium, glomerular epithelium, mesangial cells [41] and podocytes [48]. CD59 was found on gingival epithelium [49], epithelium of the salivary gland [41], thyroid follicular cells [50], bronchial epithelium [41], squamous epithelium [41, 47], keratinocytes [51], chondrocytes [52], synovia [53], muscle cells [54], amniotic cells [55], and extravillous trophoblast [56].

**CD59 Expression in Inflammation and Infectious Disease**

Surface structures of bacteria and viruses can activate the human complement system via the alternative pathway or the lectin pathway. Antibodies binding to bacteria...
Table 2. Tissue distribution of CD59

| Blood cells | Erythrocytes [114] | Leucocytes [115] | Platelets [35] | Dendritic cells [36] |
|-------------|-------------------|-----------------|----------------|---------------------|
| Nervous system | Brain parenchyma [37] | Neurons [38–40] | Chorioid plexus epithelium [37, 39] | Ependymal cells [41] |
| | Glomerular epithelium [41] | Mesangial cells [41] | Podocytes [48] |
| | Glomerular endothelium [41] | | |
| | Salivary gland [41] | Thyroid follicular cells [50] |
| | Squamous epithelium [41, 47] | Keratinocytes [51] |
| | Chondrocytes [52] | Synovia [53] | Muscle cells [54] |
| Placental tissue | Amniotic cells [55] | Extravillous trophoblast [56] |

CRP upregulates CD59 expression in peripheral leucocytes. CRP is part of a network of mediators, which regulate CD59 expression: CRP is produced by the liver upon stimulation by interleukin-6 (IL-6). IL-6 is produced by monocytes and other cells in infection and inflammation, for example upon stimulation by LPS. LPS-stimulated monocytes in addition release IL-1 and tumour necrosis factor alpha (TNF-α). These and other pro-inflammatory cytokines can directly upregulate CD59 expression: TNF-α and IL-1 upregulated the expression of CD59 in colon carcinoma cell lines [61] and in a hepatoma cell line [62], but not in keratinocytes [51]. In endothelial cells, TNF-α upregulated CD59, but IL-1 downregulated CD59 expression [63]. Interferon gamma (IFN-γ) upregulated CD59 in colon cancer cells when used in low dose [61], but not with regular concentrations [61, 64]. In hepatoma cells, IFN-γ strongly antagonised CD59 upregulating effects of TNF-α or IL-1 [62]. Not only pro-inflammatory but also anti-inflammatory cytokines upregulated the expression of CD59: IL-10 was found to upregulate CD59 on monocytes [65]. These in part contradicting results need further investigations. It is likely that different experimental conditions had an impact on the cytokine secretion in these in vitro experiments. In addition, different kinds of cells or tissues indeed may show individual reaction patterns.

**CD59 and Rheumatoid Arthritis**

Rheumatoid arthritis is associated with chronic inflammation of peripheral joints. The synovial lining is infiltrated with leucocytes and, with progress of the disease, synovial cells will form the pannus, a tissue that invades and destroys the structures of the bone and the cartilage of the joint. Pro-inflammatory cytokines, immune complexes and elevated levels of complement components are present in the synovial fluid [66]. Complement and CD59 were discussed to play a role in rheumatoid arthritis and in other forms of arthritis [67–69]. These findings triggered experiments in animal models investigating the role of the MAC and of CD59 in arthritis. When osteoarthritis and synovitis were induced by trauma, mice deficient in C6, a component of the MAC, were protected against arthritis [70]; mice deficient in CD59 developed more severe arthritis and synovitis [70] or rheumatoid arthritis [71] than wild-type mice. In rat models, intra-articular blocking of CD59 by injection of a monoclonal anti-CD59 F(ab’)2 caused acute arthritis [72], whereas intra-articular administration of rat CD59 suppressed rheumatoid disease [73]. In one in vitro study, statins upregulated CD59 expression on endothelial cells cultured under hypoxic conditions, and the authors speculated that by this mechanism, statins exert an anti-inflammatory effect in rheumatoid arthritis [74]. In vivo studies in humans are missing so far.

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and viruses activate the classical pathway. A large number of C3b molecules may spread onto the surrounding tissues and nearby cells, ready to build a C5 convertase and activate the MAC. CD59 protects the cells from lysis by the MAC, but this protection is not absolute as we know from the transfusion of ABO-incompatible erythrocytes [57]. If the activation of the MAC is massive, protection by CD59 can be overruled and cells will be damaged. From the perspective of the host, it would be favourable if endothelial cells and the cells in the neighbourhood of a local infection or inflammation could upregulate the number of CD59 molecules on their membranes. Lipopolysaccharide (LPS) from the cell wall of gram-negative bacteria, for example, can directly upregulate CD59 expression on human monocytes [58] and on oral epithelial cells [59]. Another important regulator of CD59 is the C-reactive protein (CRP), an acute-phase protein that increases in plasma during inflammation. In a computational analysis of 491 individuals of the Estonian biobank cohort, high CRP levels were strongly correlated with activation of the CD59 gene in leucocytes [60]. The authors additionally performed cell culture experiments and confirmed that
**CD59 and Age-Related Macular Degeneration**

Age-related macular degeneration (AMD) is the most common cause of blindness in industrialized nations [75]. Atrophic changes of the RPE and photoreceptors cause progressive loss of vision. The cause and the pathogenesis of AMD are not well understood. Risk factors are age, genetic predisposition, oxidative stress and smoking [76]. Accumulation of oxidative damage and inflammation are thought to injure the retinal cells [77]. With normal ageing, increasing numbers of so-called drusen can be found in the retina: deposits of lipids and proteins (lipofuscin) between the cells of the RPE and the Bruch’s membrane [78]. In addition to the expected age-related, smaller (<63 μm) drusen, increased numbers of large (>125 μm) drusen were found in AMD patients [79]. Drusen contain complement proteins and CD59 protein [80], and choroid cells carry complement proteins including the MAC on their surface [79], implicating a role for the complement system in the pathogenesis of AMD [81]. In 2005, several groups identified a common variation of complement factor H, Y402H, as a risk for AMD [82–84]. It was discussed that the variant factor H might be less efficient in inhibiting activated C3 molecules bound to the cell membrane and, thereby, allows increased formation of MAC. MAC deposition on the RPE and the choriocapillaris causes damage to these cells and promotes the development of AMD [84]. Cells of the RPE in AMD-affected regions of the retina showed a markedly decreased expression of CD59 [80]. Exogenous triggers such as oxidative stress [43] or oxidised lipoproteins [80] can cause the retinal cells to release CD59 by shedding or by transfer of CD59-containing exosomes to the subretinal space where CD59 might be integrated into the drusen [80]. Retinal cells partially or completely depleted of CD59 are susceptible to damage or lysis consequent to MAC deposition. A role for CD59 in the development of AMD was confirmed in animal models [85, 86] and therapeutic attempts were made to provide the RPE of AMD animals with soluble or with membrane-targeted recombinant human CD59 proteins [85, 87]. For humans, several clinical trials investigating complement inhibitors for AMD patients are ongoing [88]. One of these trials (NCT03144999) investigates whether an adenovirus vector, injected intravitreally, can cause the retinal cells to upregulate expression of CD59. No results have been published to date.

**CD59 and Cancer**

The complement system is fighting tumour cells. It can be activated via all 3 pathways: natural occurring IgM antibodies directed against tumour-specific antigens can bind to tumour cells and start the classical pathway [89, 90]. Mannose-carrying polysaccharide structures on glioma cells activated the lectin pathway [91]. Virus-transformed B cell lymphoma cells and HIV-infected T cells may present structures of the virus capsule in the cell membrane which start the alternative pathway [92, 93]. From the perspective of a tumour cell, it would be advantageous to protect itself by increased expression of CD59 in order to evade lysis by the complement system. Thus, upregulation of complement inhibitory molecules, including CD59, on the surface of tumour cells was interpreted as an evasion mechanism. Squamous cell cancer expressed increased CD59 as compared to normal cells [94]. Increased expression of CD59 on breast cancer correlated with higher numbers of lung metastases and with poorer prognosis [95]. Increased expression of CD59 correlated also with poorer prognosis in oesophageal cancer [96]. Colon cancers with grade III and IV in TMS staging and colon cancer cells with low differentiation showed increased expression of CD59 [97]. It was further observed that increased expression of CD59 made oesophageal cell lines resistant to radiation therapy [96], whereas silencing of CD59 expression with siRNA made the tumour cells more sensitive to chemotherapy [98].

We have seen in a previous section that cytokines can upregulate the expression of CD59 by different tumour cells and cell lines. It is possible that upregulation of CD59 by tumour cells is not a property newly acquired with the malignant transformation. Tumours can activate the immune system which tries to eliminate the malignant cells by antibodies and complement, but also by monocytes, T cells, and natural killer cells. These leucocytes may release cytokines, including TNF-α, IL-1, and IFN-γ, producing an inflammatory milieu which drives tumour cells, but also other cells, to upregulate CD59 expression. Further studies are needed to clarify the role of CD59 in tumour disease and to evaluate the risks and chances of targeted CD59 downregulation in tumour therapy.

**Deficiency of CD59 Is Associated with Severe Disease**

*Acquired Deficiency of CD59 on Blood Cells*

PNH is an acquired disease characterised by chronic intravascular and extravascular haemolysis and caused by the inability of PNH cells to control activated complement components (for details see [99]). The released free haemoglobin scavenges nitric oxide (NO) which functions to maintain smooth muscle relaxation. The depletion of NO contributes to smooth muscle dystonia, which causes PNH manifestations like oesophageal spasms, abdominal pain and erectile dysfunction. Activated complement components like C5a, parts of the inner membrane of the lysed erythrocytes, activated platelets, and other factors cause a pro-inflammatory and pro-thrombotic state. Thromboses are a common manifestation of
PNH and are the major cause of mortality in PNH patients [100–102].

Most patients with PNH carry an expanding haematopoietic stem cell clone with an acquired mutation of the phosphatidylinositol glycan class A (PIGA) gene [16]. The PIGA gene is involved in the synthesis of the GPI anchor biosynthesis, and the mutations found in PNH patients disturb or abolish the production of GPI. In consequence, the expression of GPI-anchored cell membrane proteins including the complement regulatory proteins CD55 and CD59 on erythrocytes, leucocytes and platelets deriving from this stem cell is markedly decreased or completely lacking. The deficiency of CD55 and CD59 makes the cells vulnerable to attacks of the complement system: on healthy cells, CD55 is crucial for the inactivation of the C5-convertases of all 3 pathways and, thereby, counter-regulates the formation of pro-inflammatory C5a and of C5b, the first component of the MAC. CD59 is the only membrane-bound inhibitor of the MAC and, therefore, lack of CD59 on PNH cells mainly contributes to intravascular haemolysis, the dominant clinical manifestation of PNH, and its sequelae pro-thrombotic state and smooth muscle dystonia [100].

The important role of CD59 for the clinical manifestations of PNH can be estimated by the therapeutic success of the monoclonal antibodies eculizumab and ravulizumab [103, 104]. Both antibodies bind to C5 and inhibit the cleavage into C5a and C5b, i.e., they block the initiation of the terminal pathway, while CD59 blocks the last step of the terminal pathway, the assembly of C8 and C9 molecules. The mechanisms of action of C5-blocking antibodies and of CD59 are different, the effect for the erythrocytes is very similar: the MAC cannot be assembled and the cell will not be lysed. In a study using eculizumab for therapy of PNH patients for an observation period of 26 weeks, intravascular haemolysis was nearly stopped com-

Table 3. Signs and results of neurologic, radiologic and pathologic examination of patients with congenital CD59 deficiency

| Genetic variant | Ethnic origin | Number of patients | Onset of disease | Major signs observed during recurrent episodes or at presentation | Major results of radiologic, neurologic, or pathologic examination found with 1 or more children |
|-----------------|---------------|--------------------|-----------------|---------------------------------------------------------------|--------------------------------------------------------------------------------------------------|
| c.123delC      | Japanese      | 1                  | 13 years        | Haemolysis, cerebral infarctions                              | –                                                                                                 |
| c.361delG      |               |                    |                 |                                                              |                                                                                                   |
| c.266G>A       | North-African | 3                  | 3–7 months      | Haemolysis, demyelinating polyneuropathy, weakness            | ENMG: results indicative of demyelinating polyneuropathy                                          |
|                | Jewish        |                    |                 |                                                              | Biopsies: thinning of myelin, reduction in fibre number, demyelination                            |
|                |               | 2                  | 3–5 months      | Flaccid paralysis lower limbs, flaccid tetraparesis, respiratory insufficiency, haemolysis | ENMG: results indicative of demyelinating polyneuropathy                                          |
|                |               |                    |                 |                                                              | MRI: cortical ischaemic infarctions                                                              |
|                |               |                    |                 |                                                              | VEP: retinal and optical nerve damage                                                             |
| c.146delA      | Turkish       | 3                  | 1–7 months      | Polyneuropathy, tetraparesis, muscle atrophy, areflexia, bilateral ptosis, respiratory insufficiency, haemolysis | ENMG: reduced conduction velocity                                                                  |
|                |               |                    |                 |                                                              | Demyelinating polyneuropathy                                                                      |
|                |               |                    |                 |                                                              | MRI: haemorrhagic lesions, cerebral infarctions                                                   |
|                |               |                    |                 |                                                              | Biopsy: damaged endothelium of brain vessels, progressive stenoses                                 |
| c.146A>T       | Turkish       | 3                  | 6–11 months     | Hemiparesis, muscle atrophy, nystagmus, haemolysis           | MRI: cerebellar haemorrhagic lesion                                                                |
|                |               |                    |                 |                                                              | ENMG: axonal neuropathy and demyelination                                                         |
|                |               | 2                  | <10 years       | Dysarthric speech, horizontal nystagmus, muscle atrophy, urinary incontinence | MRI: cortical and cerebellar lesions, myelopathy                                                   |
| c.323C>A       | Turkish       | 1                  | 1 year          | Convulsions, hemiparesis, paralysis of cranial nerves         | MRI: thalamic, cerebellar, temporal, spinal lesions                                                |
| c.85T>G        | Iranian       | 1                  | 15 months       | Facial oedema, paraesthesia, weakness                         | MRI and ENMG: demyelinating processes central and peripheral                                        |

MRI, magnetic resonance imaging; ENMG, electroneuromyography; VEP, visually evoked potentials.
ditional children were diagnosed (Table 3), 3 of them post disorders to the diagnosis of CD59 deficiency. Twelve ad-
care of children with haemolysis and polyneuropathic
This publication draws the attention of physicians taking
by flaccid paralysis predominantly of the lower limbs.
suffered from progressive muscle wasting accompanied
demyelinating polyneuropathy-like disease [108]. They
deficiency presented with severe chronic inflammatory
1 and 4.5 years of age from 4 unrelated families with CD59
neuropathy, in contrast to most of the other patients with
codon [11]. This patient did not show signs of peripheral
ble 1), which leads to a frameshift and a premature stop
gosity for the single nucleotide deletion c.123delC (Ta-
and vascular endothelium, also did not express CD59.
The investigation of the genes revealed homozy-
chores protein CD55. Other cells of the patient, such as
fibroblasts, keratinocytes, secretory cells of several glands,
and vascular endothelium, also did not express CD59.
The investigation of the CD59 genes revealed homozy-
gosity for the single nucleotide deletion c.123delC (Ta-
le 1), which leads to a frameshift and a premature stop
codon [11]. This patient did not show signs of peripheral
neuropathy, in contrast to most of the other patients with
CD59 deficiency reported thereafter. It lasted until 2013,
when the next patients were reported: 5 children between
1 and 4.5 years of age from 4 unrelated families with CD59
deficiency presented with severe chronic inflammatory
demyelinating polyneuropathy-like disease [108]. They
suffered from progressive muscle wasting accompanied by
flaccid paralysis predominantly of the lower limbs.
This publication draws the attention of physicians taking
care of children with haemolysis and polyneuropathic
disorders to the diagnosis of CD59 deficiency. Twelve ad-
ditional children were diagnosed (Table 3), 3 of them post mortem [109, 110], and the histories of early deceased
relatives who had shown similar symptoms were reviewed
[13, 111].
Most of these patients had chronic haemolysis and se-
vere neurological disease. Damage of endothelial cells in
small vessels was observed [110]; some patients developed
acute renal failure [12, 108, 109]. Demyelination of
Peripheral sensory and motor nerves led to weak reflexes
or areflexia, muscle weakness and difficulties or inability
to walk, and they required mechanical ventilation [12, 13,
112]. Further, peripheral hypoesthesia [14] and urinary
incontinence [111] were observed. Demyelinating pro-
cesses in the central nervous system, ischaemic infar-
tions or haemorrhagic events impaired the cognitive abili-
ties and mental development including speech. The ret-
a and the optical nerve were involved, and some of the
children developed difficulties to swallow. Half of the
children developed hemiparesis or tetraparesis. Many of
the neurological symptoms exacerbated after vaccination
or infection, confirming an important role of comple-
ment and of the immune system in CD59 deficiency. When
the activation of the immune system had declined,
sometimes a partial remission was observed, but in the
long run, the disease progressed in all children and 6 of
them had died at the time their case was published.

**Congenital CD59 Deficiency**

CD59 is the only membrane-bound inhibitor of the
MAC protecting the host's cells when the complement
system becomes activated, and we have seen in the previ-
ous section that loss of CD59 on only a part of the blood
cells can cause severe and life-threatening disease. It is
hard to imagine that a complete loss of CD59 on all cells
and tissues is compatible with life. Indeed, inherited ho-
mozygosity for alleles causing a complete CD59 deficien-
cy causes devastating illness. In 1990, a 22-year-old man
with isolated CD59 deficiency was reported [25]. He had
a 9-year history of recurrent haemolysis and suffered from
hemiplegia after cerebral infarction. His erythro-
cytes were CD59 deficient but expressed the GPI-an-
chored protein CD55. Other cells of the patient, such as
fibroblasts, keratinocytes, secretory cells of several glands,
and vascular endothelium, also did not express CD59.

The lessons learned from PNH patients suggested an
off-label use of the monoclonal antibody eculizumab in
these patients. The first patient treated with eculizumab
[12] showed immediate control of haemolysis. At start of
therapy, the girl had a flaccid paralysis, could not swallow
and needed mechanical ventilation. Six weeks after start
of therapy with eculizumab, remission of neurological
symptoms started, and after 39 weeks, the 5.5-year-old
girl was no longer ventilated, she could swallow and stand
without assistance (albeit not walk). Improvement of
neurological disease was seen with all patients treated
with eculizumab. The ability to swallow returned [112,
113], muscle strength improved [14, 111–113], and some
children learned to stand with support [14, 113]. We
hopefully will learn about the long-term effect of C5-
blocking therapy in these children, including break-
through events and impaired defence against bacterial in-
fecions. We hopefully also will learn to what extent neu-
roplasticity can reverse damage of the peripheral nerve
system and the brain in the children diagnosed so far.
Paediatricians are now aware of CD59 deficiency as a pos-
sible cause of polyneuropathy and an early start of thera-
py may ameliorate the severity of the disease in future
patients.

**Conclusion**

A clear role for CD59 in disease has been established
for PNH and congenital CD59 deficiency, where lack of
CD59 expression causes severe and life-threatening dis-
ease. In congenital CD59 deficiency, children suffer from
severe neurological disease and die at a young age. In the
recent years, therapy with C5-blocking monoclonal anti-
bodies was started for most of the reported children,
which seemed to stop progression and even improved
their status but did not restore their health. No follow-up
and no reports on long-term efficiency have been published so far.

Surprisingly little evidence for the role of CD59 in other diseases is available. The contribution of CD59 to rheumatoid arthritis and to AMD has been investigated in animal models, but clinical studies have not been published. The investigated cells in these diseases, e.g., patients’ synovial cells or retinal cells, are not easily accessible. Mediators released in inflammation or in infectious disease can regulate expression of CD59, presenting the investigators the hen and egg dilemma: is, e.g., down-regulation of CD59 cause or consequence of disease? These circumstances make the research complex and time consuming, but the important protective function of CD59 and the lack of substitute inhibitors should encourage research on CD59 and its role in inflammatory diseases.

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Conflict of Interest Statement

The author has no conflicts of interest to declare.

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C.W. wrote the manuscript.

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