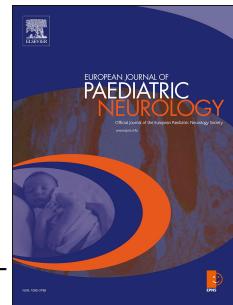


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CD59 deficiency presenting as polyneuropathy and Moyamoya syndrome with endothelial abnormalities of small brain vessels



Christian Kleemann, Janbernd Kirschner, Sandra Ammann, Horst Urbach, Olaf Moske-Eick, Barbara Zieger, Myriam Ricarda Lorenz, Klaus Schwarz, Soroush Doostkam, Stephan Ehl, Rudolf Korinthenberg

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1 **CD59 deficiency presenting as polyneuropathy and Moyamoya syndrome with**
2 **endothelial abnormalities of small brain vessels.**

3 Christian Klemann^{1,2,3}, Janbernd Kirschner^{2,4}, Sandra Ammann^{1,5}, Horst Urbach⁶,
4 Olaf Moske-Eick^{6,2} Barbara Zieger², Myriam Ricarda Lorenz⁷, Klaus Schwarz^{7,8},
5 Soroush Doostkam⁹, Stephan Ehl^{1,2}, Rudolf Korinthenberg^{2,4}

6 ¹Center for Chronic Immunodeficiency (CCI), Medical Center – University of
7 Freiburg, Faculty of Medicine, University of Freiburg, Germany.

8 ²Center for Pediatrics, Medical Center – University of Freiburg, Faculty of Medicine,
9 University of Freiburg, Germany

10 ³Department of Pediatric Pneumology, Allergy and Neonatology, Hannover Medical
11 School, Hannover, Germany.

12 ⁴Center for Pediatrics, Department of Neuropediatrics and Muscle Disorders, Medical
13 Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Germany

14 ⁵Cambridge Institute for Medical Research, Cambridge Biomedical Campus,
15 Cambridge, United Kingdom.

16 ⁶Department of Neuroradiology, Medical Center – University of Freiburg, Faculty of
17 Medicine, University of Freiburg, Germany

18 ⁷Institute for Transfusion Medicine, University of Ulm, Ulm, Germany;

19 ⁸Institute for Clinical Transfusion Medicine and Immunogenetics Ulm, German Red
20 Cross Blood Service, Baden Württemberg – Hessen, Ulm, Germany

21 ⁹Institut for Neuropathology, Medical Center – University of Freiburg, Faculty of
22 Medicine, University of Freiburg, Germany

23

24 **Corresponding author:**

25 Dr. med. Christian Klemann,

26 Department of Pediatric Pneumology, Allergy and Neonatology,
27 Hannover Medical School, Hannover, Germany.

28 Email: Klemann.Christian@mh-hannover.de

29

30 Conflict of interests: none

31 **Key words:** MMD, MMS; high resolution vessel wall imaging; HR-VWI; CIPD; GBS;
32 pediatric stroke, early-onset stroke, hemolysis, hemolytic anemia

33 **Highlights:**

34 • Congenital isolated CD59 deficiency has previously been associated with
35 recurrent episodes of hemolytic anemia, peripheral neuropathy, and strokes.
36 • In this 4th patient with the p.Asp49Valfs*31 mutation in CD59 reported, brain
37 endothelium showed absent CD59 expression. Moyamoya syndrome
38 developed with contrast enhancement of the distal carotid arteries and
39 shrinkage of vascular diameter while systemic vasculitis could be excluded.
40 • Targeted therapy with eculizumab might have prevented the lethal course in
41 our patient.

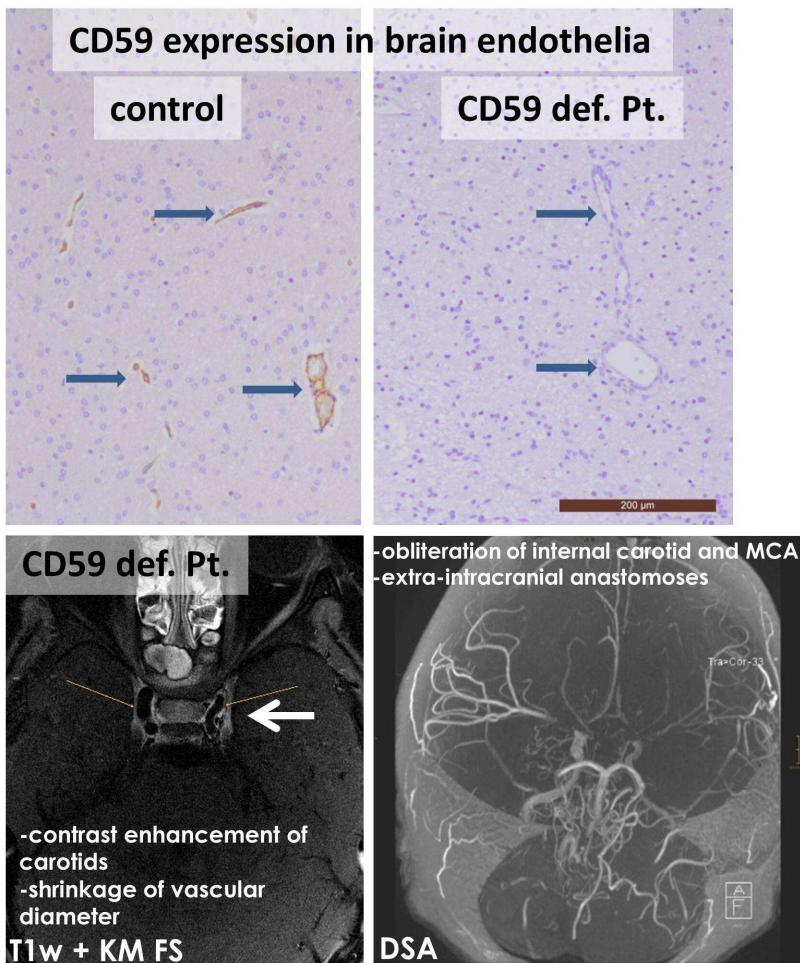
42

43 **Abstract:** (word count: 214)

44 CD59 is involved in lymphocyte signal transduction and regulates complement-
45 mediated cell lysis by inhibiting the membrane attack complex. In the cases reported
46 so far, congenital isolated CD59 deficiency was associated with recurrent episodes of
47 hemolytic anemia, peripheral neuropathy, and strokes. Here, we report on a patient
48 from a consanguineous Turkish family, who had a first episode of hemolytic anemia
49 at one month of age and presented at 14 months with acute Guillain-Barré syndrome
50 (GBS). The child suffered repeated infection-triggered relapses leading to the
51 diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP). Although
52 partly steroid-responsive, the polyneuropathy failed to be stabilized by a number of
53 immunosuppressive agents. At the age of 6 years, he developed acute hemiparesis
54 and showed progressive stenosis of proximal cerebral arteries, evolving into
55 Moyamoya syndrome (MMS) with recurrent infarctions leading to death at 8 years of
56 age. Post-mortem genetic analysis revealed a pathogenic p.Asp49Valfs*31 mutation
57 in CD59. Re-analysis of brain biopsy specimens showed absent CD59 expression
58 and severe endothelial damage. Whereas strokes are a known feature of CD59
59 deficiency, MMS has not previously been described in this condition. Therefore, we
60 conclude that in MMS combined with hemolysis or neuropathy CD59 deficiency
61 should be considered. Establishing the diagnosis and targeted therapy with
62 eculizumab might have prevented the lethal course in our patient.

63

64

65 **Graphical abstract:**

66

67 CD59 deficiency presenting as polyneuropathy and Moyamoya syndrome with
68 endothelial abnormalities of small brain vessels.

69 **Introduction:**

70
71 The complement system is a complex family of proteins with a myriad of functions,
72 including killing of target cells via the membrane attack complex (MAC). CD59 is the
73 only protein inhibitor of the terminal pathway of the complement cascade preventing
74 formation of the MAC [1]. Somatic mutations in the protein anchoring CD59 and
75 related proteins on the cell surface of erythrocytes result in paroxysmal nocturnal
76 hemoglobinuria presenting with recurrent hemolysis. However, deleterious autosomal
77 recessive germline mutations in CD59 have recently been described to cause severe
78 early-onset immune-mediated chronic neuropathy, chronic or relapsing Coombs-
79 negative hemolysis, and cerebrovascular events [2–7]. These observations,
80 summarized in table 1, are based on the 12 hitherto reported patients.

81 Moyamoya disease (MMD) is a rare, chronic, occlusive cerebrovasculopathy and a
82 known cause of pediatric stroke. The pathogenesis and etiology is largely unknown
83 despite devastating, permanent neurological disability if left untreated. MMD is
84 characterized by progressive stenosis of the intracranial internal carotid arteries and
85 their main branches and the development of compensatory collateral vessels at the
86 base of the brain vascularizing the hypoperfused brain distal to the occluded vessels.
87 Sometimes, similar clinical and radiologic signs are evident in children with other
88 medical conditions then termed Moyamoya syndrome (MMS). In this report, we
89 extend the clinical phenotype of CD59 deficiency to angiographic features of cerebral
90 vasculopathy progressing to MMS.

91

92 **Materials & methods:**

93 Informed consent for retrospective collection of patient history and clinical data as
94 well as for genetic analyses was obtained from the patient and his family members in
95 accordance with local ethics committee guidelines.

96 Biopsy material from frontal left dura and cortex was investigated by histology and
97 immunohistochemistry. After formalin fixation, conventional staining for H&E, EvG
98 and PAS were performed from the paraffin-embedded biopsy material. Antibodies
99 directed towards CD59 (BioScience, 7BIO-1B-233-C100), CD34 (Dako, M 7165) and
100 CD61 (Dako, M 0753) were used for immunohistochemistry.

101 For sequencing of CD59, 100 ng genomic DNA or cDNA corresponding to 25 ng total
102 RNA of PBMC was amplified, followed by sequencing using Big Dye Terminator v1.1
103 Cycle Sequencing Kit (Applied Biosystems, Darmstadt, Germany). Sequencing
104 products were separated on an Applied Biosystems 3130xl Genetic Analyzer. Primer
105 sequences are available upon request from K.S. Multiple sequence alignments were
106 performed at <http://www.ncbi.nlm.nih.gov/>. Databases for analyzing the frequency of
107 the variation used were SNPbase (<http://www.ncbi.nlm.nih.gov/snp>), 1000 Genome-
108 Database (http://browser.1000genomes.org/Homo_sapiens/Info/Index), EVS-
109 Database (<http://evs.gs.washington.edu>), Kaviar-Database
110 (<http://db.systemsbiology.net/kaviar/>), and ExAC-Database
111 (<http://exac.broadinstitute.org/>).

112

113 **Results:**

114 Our patient was born as the first son of healthy consanguineous Turkish parents (**fig.**
115 **1A**). No relationship to previously reported Turkish patients could be established.
116 Pregnancy was uneventful; birth was complicated by meconium aspiration and
117 sepsis requiring antibiotic treatment. The patient presented at the age of 1 month
118 with an episode of hemolysis (minimal hemoglobin 7.0 g/dl) prompting an erythrocyte
119 transfusion. LDH was increased while direct and indirect Coombs tests were
120 negative. Osmotic testing of erythrocytes, Hb-electrophoresis and G6PDH were
121 normal. In the year thereafter no new episodes of hemolysis occurred and neuro-
122 cognitive and motor development were normal.

123 After the development of the independent walking capability, at the age of 14 months
124 the boy fell ill with apathy, areflexia and progressive tetraparesis including loss of
125 control of head position and dysphagia after a mild gastroenteritis. PCR for
126 Coxsackie A2 virus in stool was positive and again Coombs-negative hemolytic
127 anemia became apparent. Guillain-Barré syndrome (GBS) was diagnosed and the
128 condition improved markedly under a high dose of immunoglobins i.v. (IVIG). No
129 nerve conduction studies were performed during this episode. A broad metabolic
130 workup was negative. At the age of 17 months a relapse of the neurological
131 symptoms was again treated successfully with IVIG.

132 At the age of 27 months a severe relapse of GBS unresponsive to IVIG prompted
133 referral to our department of child neurology. CSF analysis was acellular with an
134 increased protein level (164 mg/dl, normal value 15 - 40 mg/dl) without signs of local
135 IgG synthesis. Similar results were found in repeated CSF investigations in the
136 following years. Nerve conduction studies in three nerves showed severe slowing of
137 conduction velocity (15-19 m/sec), dispersed motor action potentials with diminished
138 amplitude (0.4-0.5 mV), and a conduction block proving primary demyelination with
139 secondary axonal injury. This gave rise to a diagnosis of chronic inflammatory
140 demyelinating polyneuropathy (CIDP) and intravenous treatment with steroids was
141 initiated rapidly improving the clinical condition. Under continued treatment with oral
142 steroids the clinical course was initially satisfying without any signs of hemolysis and
143 positive neurocognitive and motor development (standing and walking few steps with
144 aids). Tendon reflexes remained absent throughout the further clinical course. Nine
145 months later, again following a febrile infection CIDP and hemolysis relapsed
146 prompting increasing the steroid dose and additional treatment with azathioprine. In
147 the following years the clinical course was characterized by numerous infection-
148 associated relapses of CIDP which responded well to pulsed treatment with
149 corticosteroids, but immunoglobulins were without lasting effect. Only after
150 introduction of mycophenolate-mofetil the neuropathy stabilized with a gradual
151 increase of the unaided walking distance from 50 to 500 meters.

152 Unexpectedly, at the age of 6 years the boy suffered an acute stroke with right-sided
153 dysesthesia and paresis. MRI showed multiple left-sided thromboembolic and/or
154 hemodynamic infarctions. With TOF-MRA on the left side severe stenosis involving
155 the carotid-T and the proximal M1 and A1-segments and signs of a fine collateral
156 network, and on the right side a distinct but less pronounced stenosis of the M1 origin
157 was found (**fig. 2A-C**). At follow-up 18 months later, progression of both left- and
158 right-sided stenoses, and on high-resolution Vessel-Wall Imaging (HR-VWI) diffuse
159 and circular enhancement of arterial walls affecting the distal ICA and proximal M1-
160 and A1-segments with shrinkage of the vessel diameter were shown (**fig. 2D-E**).
161 Systemic vasculitis diseases were excluded by whole body MRI, PET scan, and
162 repeated blood works including repeatedly normal von Willebrand factor antigen and
163 activity, factor VIII activity and normal D-Dimers (in episodes of absent hemolysis). A
164 combined meningeal and brain biopsy did not confirm an inflammatory process but
165 showed a severely damaged intima of blood vessels, as indicated by a loss of the

166 endothelial marker CD34, (**fig. 3A**) and an aggregation of platelets shown by the
167 immunoreactivity for the platelet marker CD61 (**fig. 3B**). Rituximab along with
168 steroids, antithrombotic treatment and MMF initially seemed to stabilize the
169 vasculopathy, but during the following year the arterial stenoses showed further
170 progression despite additional aggressive treatment with cyclophosphamide.
171 Eventually this progression resulted in the occlusion of most large cerebral arteries
172 but only a faint basal collateral network. Under the diagnosis of MMS and due to
173 repeated TIAs and minor strokes burr-hole trepanations and synangioses were
174 performed resulting in a clear cortical collateral network (**fig. 2F**). However, despite
175 these measures and maximal care the boy died at the age of 8 years due to multiple
176 malignant cerebral infarctions (**fig. 2G**).

177 Genetic analyses investigating known genes predisposing for Moya-Moya disease
178 proofed normal. Years later, following recently published reports of chronic
179 neuropathy, hemolysis and recurrent brain ischemic infarctions in pediatric patients
180 due to a germline CD59 deficiency, a post-mortem genetic investigation revealed a
181 previously reported homozygous point mutation at c.146delA (hg19, NM_203330) on
182 Exon 5 of CD59 (**fig. 1B**). This deletion leads to a frameshift at position 49
183 (p.Asp49Valfs*31) with a premature stop. The variation was not listed in SNPbase,
184 1000 Genome-Database, EVS-Database, Kaviar-Database, and ExAC-Database.
185 Both parents and the sister were heterozygous for the mutation.

186 Educated by the genetic analysis, a reanalysis of the brain and dural biopsies
187 showed subacute cerebral infarction with macrophages and capillary proliferation.
188 Several cerebral and meningeal blood vessels showed severe endothelial damage
189 with platelet aggregation both inside and outside the infarcted areas.
190 Immunohistochemically analysis of brain tissue for CD59 expression showed a
191 complete absence of CD59 staining when compared to a healthy control (**fig. 3**
192 **C&D**).

193 **Discussion**

194 CD59 (also known as MAC-inhibitory protein, membrane inhibitor of reactive lysis,
195 or protectin) is a complement regulatory protein linked to the cell surface by a GPI-
196 anchor protein [1]. Somatic mutations in hematopoietic stem cells affecting the GPI
197 anchor of several proteins reduce, amongst other proteins, the expression of CD59
198 leading to paroxysmal nocturnal hemoglobinuria (PNH) [8]. PNH is characterized by
199 Coombs-negative hemolytic anemia due to the lack of inhibition of the complement
200 cascade [8]. About half of all PNH patients additionally suffer of thrombosis, including
201 cerebral venous thrombosis in about 4 % of patients [8]. Anecdotal reports have
202 described that besides acquired mutations in GPI-anchors - and thus secondary lack
203 of CD59 – germline mutations in *CD59* can cause PNH [2,3]. In contrast to PNH,
204 germline *CD59* mutations affect all cells of the body and thus the more severe
205 phenotype is comprehensible. Recent reports of inherited *CD59* deficiency leading to
206 early-onset CIDP, coombs negative hemolytic anemia, and strokes led us to
207 reanalyze post mortally the case of a boy of Turkish descent with similar
208 presentation. We identified the 4th patient reported with a homozygous
209 p.Asp49Valfs*31 mutation (**fig. 1**) in addition to the 8 reported patients with other
210 mutations in *CD59* (**tbl. 1**). Of note, no relationship to the other affected Turkish
211 patients could be established over the past 4 generations, albeit this does not
212 contradict the presence of a founder mutation in the Turkish population.

213 Although at first sight the combination of hemolytic anemia, recurrent polyneuropathy
214 and cerebrovascular disease sounds quite uniform in all reported patients with
215 congenital *CD59* deficiency, at a closer look there are some remarkable differences
216 even between patients with the same mutation that are probably due to variable
217 pathophysiological pathways depending on the genetic background or on exogenous
218 influences. With the exception of the first reported Japanese case all patients
219 suffered from usually very early onset, severe, chronic, relapsing-remitting
220 polyneuropathy that in some of them lead to severe disability and even death (**tbl.1**).
221 In our patient as well as in the cases reported by Nevo et al., Ben-Zeev et al., and
222 Höchsmann et al. electrophysiological criteria showed that the neuropathy was
223 clearly of the classical demyelinating CIDP type with secondary axonal damage,
224 whereas the cases of Haliloglu et al. suffered from primary axonal neuropathy (in one
225 case with secondary demyelination) [4–7]. We conclude that *CD59* deficiency can

226 lead to a primary insult either at the Schwann cell or to the axon itself.
227 Pathophysiologically, CD59 deficiency might increase the vulnerability of spinal roots
228 and peripheral nerves due to diminished protection from the MAC; a previous *in vitro*
229 study demonstrated protection from complement-mediated lysis of neurons when
230 CD59 expression was increased [9]. Alternatively, autoimmunity could be causative,
231 as experimental investigations in mice lacking CD59 have shown an increased
232 susceptibility for autoimmune-phenomena [10]. Clinically, the occurrence of CIDP or
233 chronic axonal neuropathy already in infancy is extremely rare so in such cases
234 CD59 deficiency should be considered as being disease causing.

235 Not all cases with CD59 deficiency reported in the literature have suffered strokes
236 (**tbl. 1**). The affected children might have been too young at the age of reporting, but
237 this seems improbable for the 13 to 55 years old cases in the North African Jewish
238 families of Nevo et al [4]. If reported the strokes have usually been diagnosed by MRI
239 showing supra- or infratentorial infarctions due to assumed thrombo-embolic events
240 in the anterior or posterior cerebral circulation (**tbl. 1**). In one case hemorrhagic
241 stroke due to an occlusion of the PICA (posterior inferior cerebellar artery) has been
242 demonstrated by MR-angiography [7]. In contrast, serial MRI, TOF-MRA, HR-VWI
243 and DSA show relentless progression of stenoses of the proximal cerebral arteries at
244 the Circulus of Willisii in our patient and thus MMS was diagnosed (**fig. 2**).
245 Moyamoya (meaning a "hazy puff of smoke" in Japanese) is the term for a radiologic
246 finding of progressive intracranial vascular stenoses of the distal internal carotid
247 arteries and the proximal medial, anterior and less frequently posterior cerebral
248 arteries associated with enlarged collateral supply via the lenticulostriate and
249 thalamoperforating arteries and in later stages leptomeningeal and transdural arteries
250 [11–13]. Strokes and epileptic seizures constitute the prevailing presentation in
251 childhood [12]. The etiology of Moyamoya is multifactorial and largely unknown.
252 'Idiopathic Moyamoya disease' (MMD) is considered to be an entity to be separated
253 from secondary occurrences termed 'Moyamoya syndrome' (MMS). In far-eastern
254 countries the largest part of idiopathic cases is caused by a single mutation in the
255 *RNF213* gene. Other hereditary factors comprise mutations in *ACTA2*, *TIMP2*,
256 *GUCY A3*, *COL4A1* or *MOPD2*. MMS is associated with Trisomy 21,
257 Neurofibromatosis type 1, Alagille syndrome, radiotherapy, cerebrovascular
258 atherosclerosis, cerebral vasculitis and others [12, 13]. A single case of MMS has

259 been reported in the context of PNH, but whether pro-inflammatory or pro-thrombotic
260 mechanism were causative remained elusive [14].

261 Histologically, MMD and MMS are characterized by focally thickened vascular intima
262 due to proliferation of endothelial and smooth muscle cells, loss of muscle cells of the
263 media, and dilated or irregular-shaped vessel lumen [11–13]. Novel neuroradiological
264 techniques allow to consider not only the vessel lumen but also the vessel wall
265 [15,16]. However, the role of contrast-enhancement of the arterial wall in MMS is not
266 uniformly agreed on. With high resolution vessel wall imaging (HR-VWI) Ryoo et al.
267 found diffuse and circular enhancement in the arterial walls of the stenotic segments
268 in 90% of 32 MMD cases, whereas Kim et al. observed focal enhancement in only 2
269 of 7 cases [17,18]. Diffuse contrast enhancement associated with swelling of the
270 arterial wall is the radiological hallmark of acute vasculitis, as opposed to
271 cerebrovascular atherosclerosis which is characterized by focal and eccentric
272 deposition of plaques, hemorrhage and contrast enhancement [16]. Contrast
273 enhancement in cases of MMS could be an unspecific sign of an inflammatory
274 pathophysiology, and following recent reviews only the lack of swelling of the whole
275 vascular wall with increase of the vascular diameter could be an argument to
276 differentiate MMS from acute vasculitis [19–21]. It should be emphasized that
277 development of collaterals is not pathognomonic for idiopathic MMD and could also
278 represent MMS due to an unspecific reaction of the stenosis of the proximal
279 intracerebral arteries in progressive large vessel CNS vasculitis. In our patient
280 however, systemic vasculitis work-up was negative, including repeatedly normal
281 serum markers and lack of inflammatory changes in the brain- and meningeal biopsy.
282 In line with these findings, aggressive immunosuppressant treatment failed to control
283 the disease. Antiplatelet therapy may have extended the time without
284 thromboembolic events, but finally failed also to prevent the recurrent infarction in the
285 final stage of the disease because of progressive stenosis of the cerebral arteries.
286 Eventually, these investigations as well as the clinical and neuroradiological course
287 led to the diagnosis of MMS, which is now post-mortemally explained by CD59
288 deficiency

289 Concerning a possible pro-thrombotic component, intravascular hemolysis resulting
290 in depletion of nitric oxygen might have activated the platelets and endothelium [1].
291 However, the neuroradiological and haemostaseological investigations were not

292 compatible with local thrombotic disease which would be the hallmark in PNH. MMS
293 is known to be associated with intimal and endothelial dysfunction [13]. In CD59
294 deficiency chronic or acute hemolysis might trigger leukocyte- and endothelial
295 dysfunction promoting an inflammatory component in the vasculopathy which could
296 give rise to the observed contrast enhancement of vessel walls. Furthermore, it
297 seems possible that the cerebral events are a direct consequence of the lack of
298 CD59 on the cerebral endothelium making it vulnerable to disruption by the
299 complement system (fig. 3).

300 Recognizing the combination of early onset hemolysis, CIDP and stroke would have
301 prompted further diagnostics including PNH flow cytometry. With this, lack of CD59
302 expression while other GPI-anchored proteins are normally present would have
303 enabled a timely diagnosis [7]. Therapeutically, targeted complement inhibition with
304 the anti-C5 monoclonal antibody eculizumab appears to be a promising treatment
305 option also for CD59 deficiency [6,7].

306 In summary, this case expands the clinical spectrum of autosomal-recessive CD59
307 deficiency syndrome to radiologic findings of MMS. We conclude, that our case
308 emphasizes the need for early diagnosis of CD59 deficiency in young children with
309 hemolysis and chronic neuropathy as treatment with eculizumab could positively
310 influence the clinical course.

311

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321

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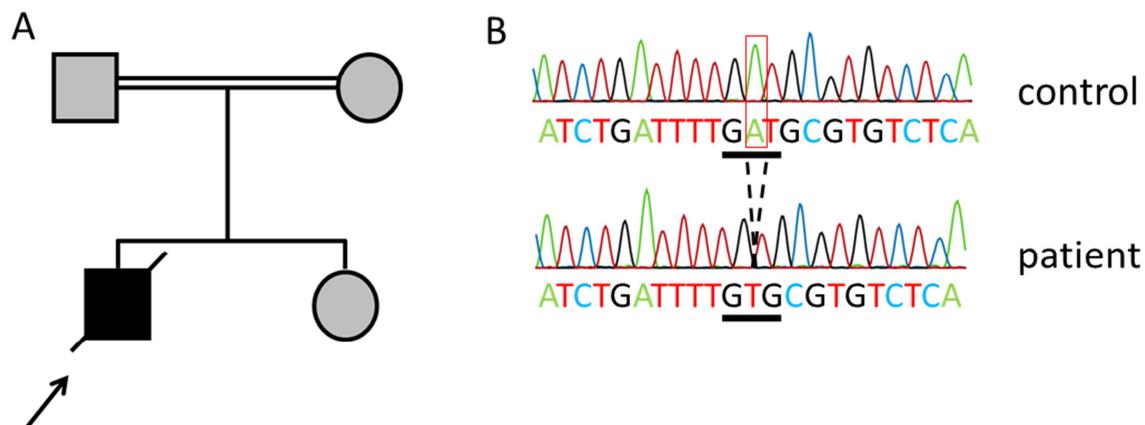
385 [21] Choi YJ, Jung SC, Lee DH. Vessel Wall Imaging of the Intracranial and

386 Cervical Carotid Arteries. *J Stroke* 2015;17:238–55.

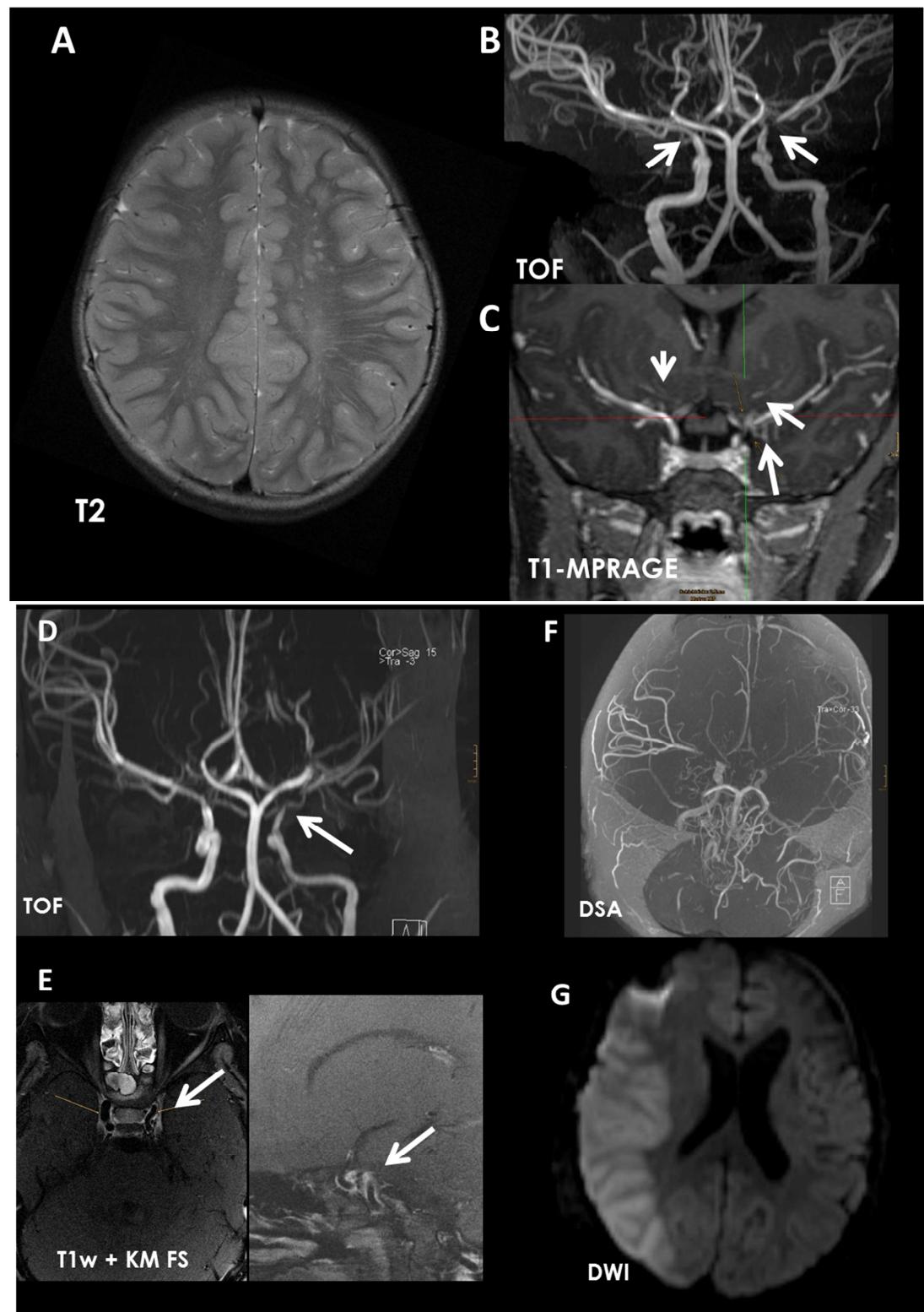
387 doi:10.5853/jos.2015.17.3.238.

388

389

390 **Figures:**

399

Figure 2

400

401

402 **Legend Figure 2:**

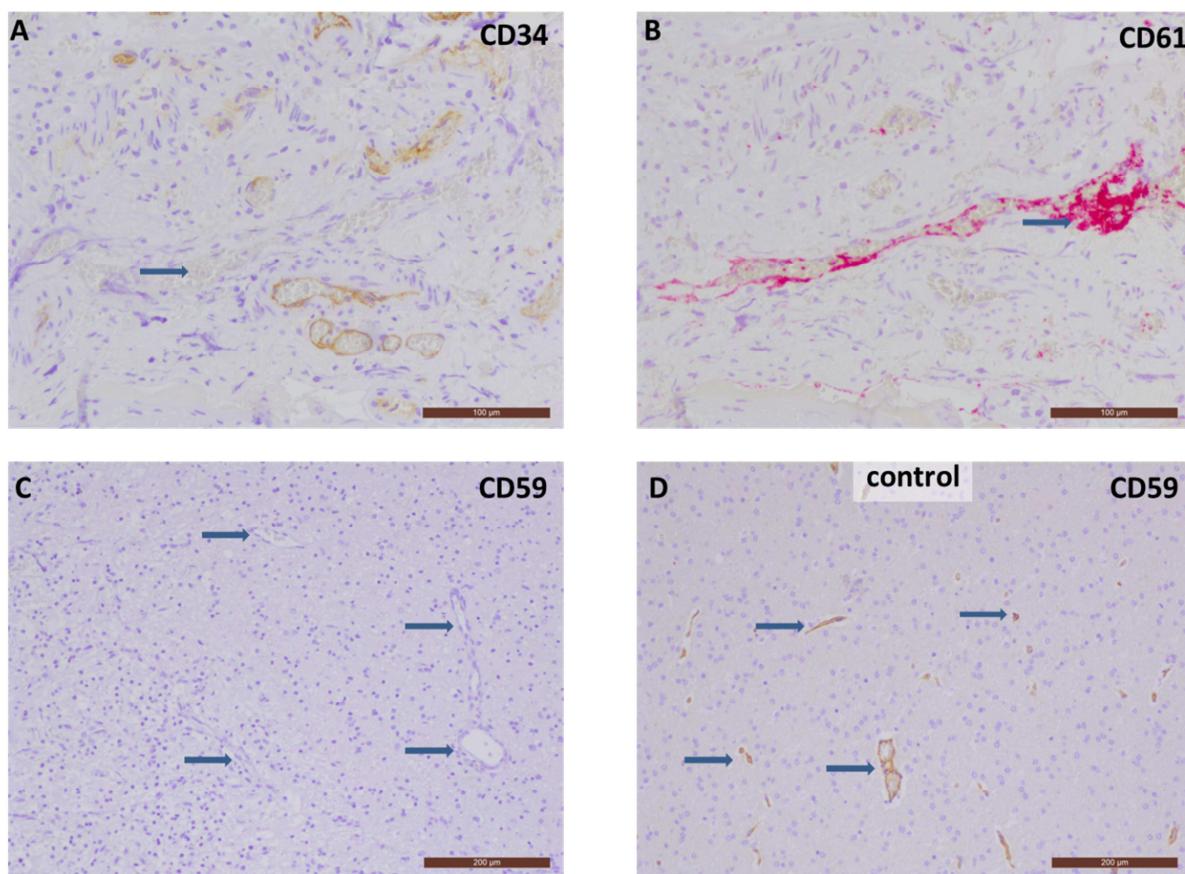
403 A-C) MR imaging at age of 6 yrs.: A) An axial T2-weighted image shows multiple
404 lesions in the left centrum semiovale. B) 3D-TOF-MRA shows severe stenosis of the

405 carotid-T on the left and moderate stenosis on the right side. C) The arrows in C
406 point to enlarged lenticulostriate arteries indicating the Moyamoya pattern

407 D-E) MR imaging at age of 7 yrs.: D) 3D TOF-MRA shows progressive stenosis on
408 both sides. E) 3Tesla vessel wall imaging shows distinct diffuse contrast
409 enhancement of the distal carotid arteries with shrinkage of vascular diameter.

410 F-G) MRI imaging at age of 8 yrs. 1 month: F) 3D TOF show complete obliteration of
411 the distal internal carotid and proximal MCA on both sides and extra-intracranial
412 anastomoses after multiple synangiosis operations. G) DWI-MRT shows severe
413 atrophy on the left after repeated infarctions and a recent complete media infarction
414 on the right.

415 **Figure 3**



417 **Legend Figure 3:**

418 Serial sections were stained immunohistochemically for CD34 and CD61.

419 (A) Blood vessels with endothelial damage (arrow) show a lack of immunoreactivity
420 of CD34.

421 (B) Detection of platelet aggregates within the same vessel in the CD61 reaction.
 422 (C) The brain biopsy tissue shows a complete lack of CD59 (arrows) compared to a
 423 healthy control (D).

424

425 **Table 1:**

| Report | Yamashina 1990, Motoyama 1992 [2,3] | Nevo 2013 [4] | Ben-Zeev 2015 [5] | Höchsmann 2014 [6] | Haliloglu 2015 [7] | Current report |
|--|---|---|--|---|--|--|
| Patient # | 1 | 2-6 | 11/12 | 7 | 8-10 | 13 |
| Ethnic Origin | Japanese | North African Jewish, 4 families | North African Jewish, 1 family | Turkish | Turkish, 1 family | Turkish |
| Consanguinity | yes | 1/5 yes | no | yes | yes | Yes |
| Mutation | compound heterozygous p.Val42Serfs*38; p.Ala121Glnfs | homozygous c.266 G>A p.Cys89Tyr | homozygous c.266 G>A p.Cys89Tyr | homozygous c.146delA, p.Asp49Valfs*31 | homozygous c.146delA, p.Asp49Valfs*31 | homozygous c.146delA, p.Asp49Valfs*31 |
| Onset of disease | 13 yrs | 3-7 mo | 3-5 mo | 7 mo | 6-11 mo | 1 mo |
| Hemolysis | yes, chronic and acute | Yes | yes | yes | no/ yes, chronic/yes acute & chronic | yes, chronic and acute |
| Coombs test | not reported | not reported | not reported | not reported | negative | intermittingly positive |
| Peripheral neurological disease | none reported | Motor-sensory, recurrent, 4/5 demyelinated secondary axonal (CIPD), 1/5 primary axonal, SMRT dorsal root enhancement 2/3 | recurrent peripheral demyelinating neuropathy with conduction block (CIPD) | Demyelinating neuropathy with secondary axonal damage | 3/3 primary recurrent axonal polyneuropathy, 1/3 secondary demyelination in later course, 2/3 gadolinium enhancement of dorsal roots | Recurrent- remitting, steroid- responsive demyelinated with conduction block |
| Central neurological disease | cerebral infarction | None reported | Recurrent cerebral infarctions from age 18 mo and 5 y, retinal and optic nerve involvement | Possible brainstem infarction versus encephalitis (MRI) at age 18 mo | 1/3 supratentorial stroke at age 5y; 1/3 infratentorial hemorrhagic stroke and occlusion of PICA at age 18 mo; 1/3 no stroke up to age 4.5 y | Recurrent supratentorial infarctions from age 6 y, small vessel endothelial damage, large vessel enhancement, moyamoya |
| Others: | | 1/5 HUS like disease w/ renal failure | atypical glomerulo- nephritis, necrotic fingers | | 2/3 phototherapy as newborn necessary | |
| Treatment | not reported | IVIG, plasmapheresis, steroids, rituximab, cyclosporin | IVIG, steroids | IVIG, plasmapheresis, eculizumab | not reported/IVIG/IVIG & eculizumab | IVIG, steroids, azathioprin, MMF, rituximab, cyclophosphamid |
| Outcome | n/a | 4 alive ~5 yrs of age, 1 deceased at 3.5 yrs. | deceased at age of 8 and 2.5 yrs. | 5 yrs, improvement under eculizumab therapy | deceased at age 16 /alive ~10 yrs with mild cognitive impairment /alive ~5 yrs with global developmental delay | Deceased at age 8 years |

426

427 **Table legend:**428 **Table 1:** Summary of reported patients with CD59 deficiency.