



## Case Report

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# CD59 Deficiency in Two Bahraini Children: Clinical Profile and Outcome

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## Abstract

CD59 is an inherited autosomal recessive disorder characterized by various clinical manifestations including hemolytic anemia, neurological deficit due to recurrent stroke and chronic inflammatory demyelinating polyneuropathy like picture. CD59 is a glycoprotein encoded by CD59 gene, and expressed in various body tissues. It provides protection against complement membrane attack complex. The aim of this presentation is to describe the clinical profile of a relative rare and unique condition, which has potential therapeutic approach and the diagnosis can help for genetic counseling.

## Keywords

CD59 deficiency, Chronic inflammatory demyelinating polyneuropathy, CIDP, Eculizumab

## Introduction

Hemolytic Anemia, CD59-Mediated, with or without Immune-Mediated Polyneuropathy (HACD59) (OMIM 612300) is an autosomal recessive disorder caused by mutation in CD59 gene on chromosome 11p13 [1]. CD59 is expressed on different cell lines, including hematopoietic cells, endothelial cells, neurons, and neuroglia, retinal pigment epithelial cells and it regulates the complement system by encoding a GPI-anchored cell surface membrane glycoprotein, that inhibit the formation of the membrane-attack complex (MAC) osmolytic pore formation [2,3]. The disease manifests early in infancy (3 to 7 months) with Prevalence of < 1/1000000 (Worldwide) [1]. The disease manifestations include hemolytic anemia in the form of Paroxysmal nocturnal hemoglobinuria (PNH), relapsing-remitting polyneuropathy exacerbated by infection, generalized hypotonia and hyporeflexia affecting the lower limbs more than the upper limbs, skeletal muscle atrophy, muscle weakness, acute promyelocytic leukemia, increased CSF protein, and macular degeneration [4].

The disease manifestation of PNH is associated with risk of thrombotic arterial events, presenting as strokes [5], and acute coronary syndromes [2]. The Complex of familial phenotype of early peripheral neuropathy, recurrent CNS ischemic like strokes and retinal involvement were considered previously to be due to mitochondrial disorders [4].

## Case 1

SM is a fifteen-year-old boy following in pediatric neurology clinic for many years. The boy was a product

of full term, normal vaginal delivery with no perinatal complications; he achieved some developmental milestones initially. At the age of eleven months he was admitted with encephalopathy like picture and treated for seizure with antiepileptic medications. Later the boy gradually improved and eventually he was able to walk with left sided weakness, slurred speech and mental handicap; neuroimaging showed multiple regions of encephalomalacia, gliosis, demyelination and cortical/cerebellar atrophy, (see Figure 1 and Figure 2). He showed also features of peripheral neuropathy for which nerve conduction study revealed axonal neuropathy. Laboratory investigations for Tandem mass spectroscopy, organic acids, lactate, ammonia, prothrombotic disorders and vasculitis screen were unremarkable.

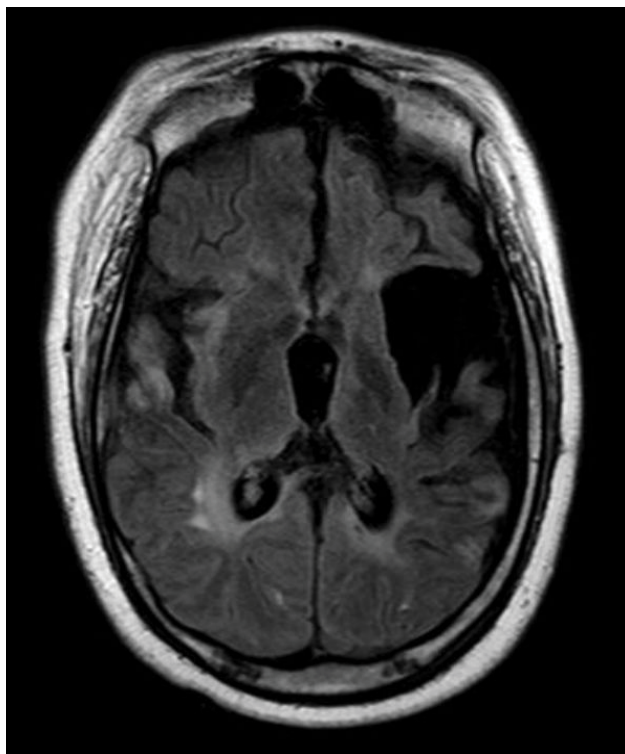
During his last admission, he presented with generalized body weakness and facial angioedema. He was lethargic, opening eyes, fixing, with poor verbal communication, left sided facial weakness, poor gag reflex; generalized body weakness with flaccid paralysis involving all extremities

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**Figure 1:** MRI brain (FLAIR) showing multiple demyelinating lesions, areas of gliosis and encephalomalacia.



**Figure 2:** MRI brain (T2WI) coronal cuts showing cortical and cerebellar atrophy.

with absent deep tendon reflexes, sensation could not be assessed. He required intubation and ventilation. MRI of the spine showed extensive cervical cord lesion from C3-C7



**Figure 3:** MRI spine (T2WI) midline sagittal plane with extensive cervical cord lesion from C3-C7.

with high intensity but without enhancement; no new brain lesion was seen, (see [Figure 3](#)). The boy had recurrent strokes previously, peripheral neuropathy but this time he has picture of acute transverse myelitis. He was managed with steroids and plasma exchange sessions, but unfortunately he remained ventilator dependent and died from sepsis.

## Case 2

EM is a six-year-old girl; a product of full term normal delivery with birth weight of 3 kilograms. By reviewing history the condition started at the age of 20 months of age as the parents reported three events of generalized body weakness at times with facial weakness with inability to stand or walk provoked by febrile illness. Case 1 is her elder brother.

On her first examination, the girl was awake and attentive, extra ocular movements were full, pupils were equal and reactive to light, no facial symmetry, and the tongue in the midline no deviation or fasciculation, saying few words, but clumsy. Motor exam showed mild hypotonia with waddling gait, and absent deep tendon reflexes. 2 years Later the girl presented with sudden onset partial visual loss, she was not able to recognize colors, she can see waving hands and was able to walk independently without hitting objects. Ophthalmological evaluation showed retinal dystrophy with suspicious retinitis pigmentosa. Her initial MRI brain was unremarkable. Nerve conduction study showed motor

neuropathy of demyelinating type. The girl's vision recovered later.

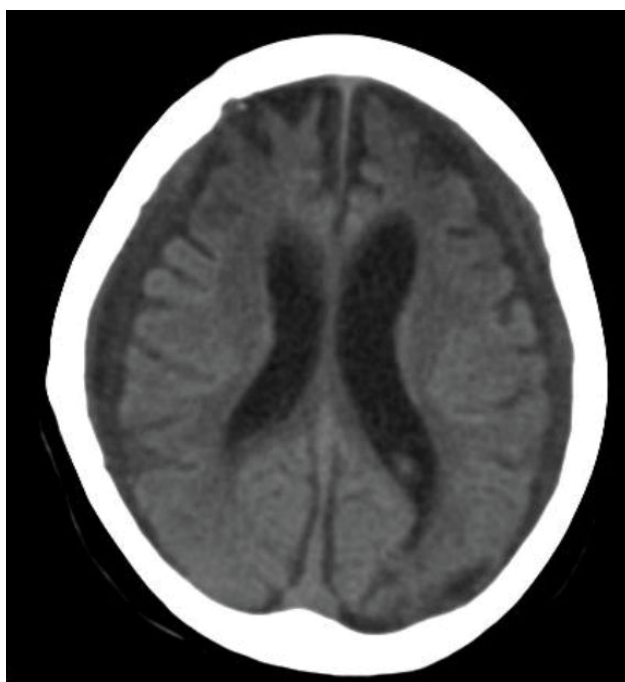
In view of these features the girl was suspected to have mitochondrial disorder and she was started accordingly on L-Carnitine and Coenzyme Q10. A trial of IVIG was planned to be given but the parents declined for social reasons.

One year later the girl presented with acute encephalopathy and recurrent seizure which required intubation, she was managed with antibiotics, Methyl Prednisolone pulse therapy & Acyclovir. Later on examination she had spastic quadriparesis and bulbar weakness. Her MRI brain showed extensive high signal intensity involving the thalami, basal ganglia, brain stem and occipital lesion bilateral. She had evidence of Epilepsia Partialis Continua and she remained on Levetiracetam and Topiramate.

She was extubated and showed minimal recovery at home, and remained bedridden.

One year later the girl presented with shallow breathing and seizure, she required immediate intubation for poor respiratory effort. The girl had further deterioration in her sensorium and went into stupor state, there was unequal pupils toward the left pupil. CT brain showed ventricular dilatation and brain atrophy, external ventricular drain inserted which was replaced later by ventriculoperitoneal shunt, (see Figure 4). The girl was in a poor neurological condition with features of minimal conscious state, subsequently she died from sepsis.

The diagnosis was confirmed by molecular DNA sequencing of CD59 gene which revealed a homozygous; c.323C>A, p.Ser108\*. Its associated with hemolytic anemia, CD59 mediated, with or without polyneuropathy. Parents were carrying the mutation in heterozygous state.



**Figure 4:** Non-enhanced CT brain revealed brain atrophy, ventricular dilatation and subdural collection.

## Discussion

Neurogenetic disorders are heterogeneous groups of neurological conditions caused by defective genes. They may affect different parts of the nervous system either central or peripheral or both. They can be associated with extra neural manifestations as well. Thousands of neurogenetic conditions have been described so far. The journey of thousand miles begins with one step, hence reaching the diagnosis of a rare disease is a cumbersome task. Begins with collecting clinical data, meticulous physical examination, reviewing the various diagnostic tests including neurophysiological and neuroimaging. Eventually, you may characterize the phenotype of the condition. The advent in genetic testing including whole exome sequencing opened venue for better diagnosis and understanding the nature of the disease. Exome sequencing is a genomic technique for sequencing all of the protein coding regions in a genome consisting about 1% of the human gene [6].

Exome sequencing can identify genetic mutation causing neurological disease which can have major implications for therapeutic approaches and testing at risk family members [7]. CD59 deficiency is frequently seen in patients with paroxysmal nocturnal hemoglobinuria (PNH).

CD59 is a glycoprotein that is linked to cell membranes by glycosyl-phosphatidyl inositol (GPI) anchor, is widely distributed, being expressed not only on peripheral blood cells but also on cells in various organs [8]. CD59 binds to both C8 and C9 in assembling membrane attack complex (MAC) to provide protection from complement mediated lysis [9]. In a study by Vedeler, et al. they found CD59 on cells *in situ* and in culture from normal nervous tissue as well as soluble in the cerebrospinal fluid (CSF). CD59 was present on schwann cells, neurons and endothelial cells in the peripheral nervous system. In the central nervous system CD59 was found predominantly on endothelial cells. There was also diffuse staining of white and gray matter of the spinal cord and the brain, presumably of microglia, oligodendrocytes, astrocytes and neurons as these cells were CD59 positive in culture [10]. CD59 deficiency is a common finding in adult patients with paroxysmal nocturnal hemoglobinuria (PNH). Chronic inflammatory demyelinating polyneuropathy (CIDP) is an immune-mediated disorder characterized by progressive or relapsing motor and sensory deficits. The estimated prevalence in children is 0.48/100000 [11]. Pediatric CIDP is generally a chronic condition, often requiring multiple modalities of treatment over time after leaving children with residual deficits even with successful treatment, a majority of patients do not have complete remission of their illness, and many need intermittent if not continuous immunomodulating treatment [12]. Haliloglu, et al. described 3 affected family members with early onset immune mediated axonal neuropathy, cerebrovascular event both in the anterior and posterior circulation, and chronic coombs-negative hemolysis, due to CD59 deficiency diagnosed through genetic testing and flowcytometry [5]. One girl died at the age of 16 due to pneumonia, second child was managed with serial IVIg courses, she was still ambulant but with some difficulties in gait. The third boy was started eventually on Eculizumab. Another case series described by



**Table 1:** Summity of reported patients with CO59 deficiency.

Report	Yamashina 1990 [13] Motoyama 1992 [14]	Nevo 2013 [12]	Ben-Zeev 2015[4]	HOchsman 2014 [3]	Haliloglu 2015 [5]	Yamathina 1950	current report
Patient#	1	2-6	11/12	7	8-10	13	2
Ethnic Origin	Japanese	North African Jewish, 4 families	North African Jewish, 1 family	Turkish	Turkish. 1 family	Turkish	Bahraini
Consanguinity	Yes	1/5 Yes	No	yes	yes	Yes	yes
Mutation	compound heterozygous p.V21425etts 38; pAla121C1nfs	homozygous c.266 G > A p.Cys89Tyr	homozygous c.266 G > A p.Cys89Tyr	homozygous c.146delA, p.Asp49Valfs x 31	homozygous c.146delA, p.Asp49Valfs x 31	homozygous c.146delA, p.Asp49Valfs x 31	Homozygous c.323C > A (p.Ser108*)
Onset of disease	13 yrs	3.7 mo	3.5 mo	7 mo	6.11 mo	1 mo	Case1:11 mo Case2:20 mo
Hemolysis	yes. chronic and acute	yes	yes	yes	no/yes, chronic/yes acute & chronic	Yes, chronic and acute	not reported
Coombs test	not reported	not reported	not reported	not reported	Negative	intermittently positive	Negative
Peripheral neurological disease	not reported	Most sensory, recurrent 4/5 demyelinated secondary axonal (CIPD), 1/5 primary axonal	recurrent peripheral demyelinating neuropathy with conduction block (CPD)	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	Relapsing peripheral demyelinating neuropathy with secondary axonal damage

<b>Central neurological disease</b>	cerebral infarction	not 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 5 yrs; 1/3 infratentorial hemorrhagic stroke and occlusion of PICA at age 18 mo; 1/3 no stroke up to age 4.5y	Recurrent supratentorial infarctions from age 6 y, small vessel endothelial damage, large vessel enhancement; moyamoya	ventricular dilatation and brain atrophy, cerebellar atrophy, encephalomalacia and recurrent cerebral infarctions from age 20mo and 3 y. retinal and optic nerve involvement
<b>Others</b>		1/5 HUS like disease w/ renal atypical failure glomerulonephritis. necrotic fingers steroids	atypical glomerulonephritis, necrotic fingers		2/3 phototherapy as newborn necessary		Case1: angioedema Case2: vision loss
<b>Treatment</b>	not reported	IVIg, Plasmapheresis, steroids, rituximab, cyclosporin	IVIg, steroids	IVIg, plasmapheresis. ecilizumab	not reported/IVIg/IVIg & ecilizumab	IVIg, steroids, azathioprine, MMF, rituximab, cyclophosphamide	Carbamazepine/ L-Carnitine and Coenzyme Q10, Keppra Topamax Biotin, Riboflavin
<b>Outcome</b>	n/a	4 alive around 5 yrs of age, 1 deceased at 3.5 yrs	deceased at age of 8 and 2.5 yrs	5 yrs, improvement under ecilizumab therapy	deceased at age 16/ alive around 10 yrs with mild cognitive impairment/alive around 5 yrs with global developmental delay	Deceased at age 8 years	Deceased at age 12 and 6

Nevo, et al. consisting of five children of north africanjewish origin from four unrelated families a homozygous missense mutation p.Cys89Tyr in CD59 was identified in all patients, which is associated with a failure of proper localization of the CD59 protein in the cell surface [12]. Recently Solman, et al. described a unique condition with recurrent episode of demyelination in the central nervous system as the only manifestation of inherited CD59 deficiency, the patient had partial response to IVIG and steroid treatment. The unfortunate siblings were both affected profoundly the boy had recurrent encephalopathy with stroke like events with partial recovery (Table 1). As mentioned earlier, extensive investigations including metabolic screen did not reveal the etiology. The boy developed myelopathy as well which made him quadriplegic and remained ventilator dependent, the boy had episodes of hematuria during his admission which was not explained as well as his facial angioedema. While his sister hematuria was explained by renal calculi. Overall, their anemia was subtle, there was no gross hemolysis. The introduction of whole exome sequencing was quiet helpful to elucidate the etiology. Both kids were treated with standard medications including IVIg and steroids and they showed partial benefit.

Although Eculizumab said to have a role in the treatment in children with CD59 mutation; their condition by the time of diagnosis was in poor situation, the girl was already in persistent vegetative state and the boy was quadriplegic for long time and suffered from recurrent infections, sepsis and pneumonia, so Eculizumab was not offered. CD59 is expressed in neurons; low neuronal expression results in neural susceptibility to MAC-driven lysis [13].

## Conclusion

CD 59 deficiency need to be considered in the differential diagnosis in a child with recurrent relapses of neuropathy, stroke and hemolytic anemia; immunomodulatory treatment need to commenced to mitigate the deficits of the disease in addition for family counselling purpose.

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