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Original article

Brain malformations associated to *Aldh7a1* gene mutations: Report of a novel homozygous mutation and literature review

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ABSTRACT

Background: The *ALDH7A1* gene is known to be responsible for autosomal recessive pyridoxine-dependent epilepsy (OMIM 266100). The phenotypic spectrum of *ALDH7A1* mutations is very heterogeneous ranging from refractory epilepsy and neurodevelopmental delay, to multisystem neonatal disorder.

Aim: The present study aims at describing the phenotype associated with a novel homozygous *ALDH7A1* mutation and the spectrum of brain malformations associated with pyridoxine-dependent epilepsy.

Methods: We conducted a literature review on the Internet database Pubmed (up to November 2017) searching for *ALDH7A1* mutations associated with brain malformations and brain MRI findings.

Results: We present the case of two siblings, children of related parents. The proband presented neonatal focal seizures not responding to conventional antiepileptic drugs. Electroencephalography showed a suppression burst pattern and several multifocal ictal patterns, responsive to pyridoxine. Brain MRI was normal. Molecular analysis by targeted next-generation sequencing panel for epileptic encephalopathy disclosed a homozygous missense mutation of *ALDH7A1*. The same mutation was then found in a stored sample of DNA from peripheral blood of an older sister dead 3 years earlier. This girl presented a complex brain malformation diagnosed with a foetal MRI and had neonatal refractory seizures with suppression burst pattern. She died at 6 months of age.

Literature review: The brain abnormalities most frequently reported in pyridoxine-dependent epilepsy include: agenesia/hypoplasia of the corpus callosum, not specific white matter abnormalities, large cisterna magna, ventriculomegaly, haemorrhages, cerebellum hypoplasia/dysplasia, and, more rarely, dysplasia of the brainstem and hydrocephalus.

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Discussion and conclusions: *ALDH7A1* mutations have been associated to different brain abnormalities, documented by MRI only in few cases. The study cases expand the clinical spectrum of *ALDH7A1* associated conditions, suggesting to look for *ALDH7A1* mutations not only in classical phenotypes but also in patients with brain malformations, mainly if there is a response to a pyridoxine trial.

1. Introduction

Pyridoxine-dependent epilepsy (PDE) is a rare autosomal recessive epileptic encephalopathy caused by mutations of the *ALDH7A1* gene (OMIM 266100),[1] encoding a protein, α-aminoadipic semialdehyde dehydrogenase, critical in the lysine degradation pathway.

Besides classical phenotype characterized by neonatal refractory epileptic encephalopathy, other neurological manifestations such as, irritability, dystonia, hypo/hypertonia, encephalopathy, hyperalertness and sleep disturbances, as well as multisystem neonatal disorders have been associated with *ALDH7A1* defects.[2] The implementation of Next Generation Sequencing (NGS) technology may help in detecting atypical or less severe phenotypes thus widening the clinical spectrum of the disease.

Recently, several different cerebral malformations associated with *ALDH7A1* mutations have been described, including delayed myelination, arachnoid cysts, non specific white matter abnormalities, hydrocephalus, agenesia/hypoplasia/dysplasia of the corpus callosum, brainstem and cerebellar hypoplasia and mega cisterna magna.[2] Other genes (e.g. PNPO and PROSC) are known to be associated with PDE; nevertheless major magnetic resonance imaging (MRI) structural abnormalities have not been related with these genes so far.[3–5]

Our work adds to the pertinent literature the case of two siblings, children of consanguineous parents, who carried a novel homozygous missense mutation of the *ALDH7A1*gene.

We describe in detail molecular clinical and neuroimaging characteristics and discuss the possible association of *ALDH7A1* mutations with severe brain malformations.

2. Methods

2.1. *Study cases*

2.1.1. *Case 1*

The proband is a boy, born at term by physiologic vaginal delivery after an unremarkable pregnancy. His birth weight was 3538 gr (50°% centile), length 51 cm (75°% centile) and head circumference 36 cm (75–90% centile). Apgar score was 9, 10 and 10 at 1′, 5′ and 10’ minutes, respectively. Prenatal ultrasounds were normal. No information about foetal movements abnormalities were reported by the mother.

At 3 hours of life he was admitted to the neonatal intensive care unit for recurrent focal seizures characterized by jerks of the limbs associated with desaturation. Anticonvulsants (midazolam and phenobarbital i.v.) were administered and the neonate was intubated and supported by high frequency ventilation. Electroencephalogram (EEG) performed at day one of life showed a suppression burst pattern and multifocal discharges.

After pyridoxine (100 mg/day i.v.) administration, EEG showed a reduction of multifocal discharges, suggesting the diagnosis of PDE. On clinical examination he showed severe axial and appendicular hypotonia with abducted lower limbs. Deep tendon reflexes and sucking reflex were decreased. In the early neonatal period, the child was also affected by congenital cytomegalovirus (CMV) infection (urinary CMV-DNA 683.000 cp/ml, plasma CMV-DNA 50.772 cp/ml), sepsis, discoagulopathy, anemia, hepatomegaly with increased levels of serum transaminases and feeding difficulties, requiring enteral tube feeding.

Cerebral ultrasound, performed at birth, showed bilateral periventricular hyperechogenicity and mild ventricular enlargement. Brain magnetic resonance imaging (MRI), which was only possible at 13 days of life due to the critical conditions, showed, on T2-weighted images, few spotted white matter hypointensities and focal left choroid plexus hemorrhage with tiny hemosiderin deposits in the occipital horns of the lateral ventricles (Fig. 1). Spectroscopic investigation (long-TE) didn't reveal significant changes of main brain metabolites.

Additional analyses, including serum ammonia, lactate, homocysteine and sialotrasferrin pattern were normal. Physical-chemical analysis of the cerebrospinal fluid (CSF) was normal, while neurotransmitter metabolites showed an increase in 3-methoxy-L-Tyrosine (1078 nmol/l, NV 24–148). Decreased level of CSF pyridoxal-phosphate (7 nmol/L, NV 14–92) and increased urinary and serum levels of Alpha Amino Adipic Semialdehyde (AASA) were found (u-AASA 177,5 umol/L, s-AASA 16,4 umol/L). Pipecolic acid was found to be elevated in urine (688,0 μmol/g Cr; NV 9,81–84,5 μmol/g Cr) and in plasma (39,04 μmol/l; NV 0,7–2,46 μmol/l).

2.1.2. Case 2

The proband's sister was born at term by vaginal delivery. Neonatal weight was 2520 gr (3% centile), length 46 cm (3% centile) and head circumference 29 cm (<3% centile). Apgar score was 9, 10 and 10 at 1′, 5′ and 10′ minutes, respectively. A second trimester ultrasound anatomy scan showed a severe brain malformation. This was then confirmed at 21 gestational weeks by foetal MRI (Fig. 2A–B), which showed a striking abnormality of supratentorial structures with apparent thalamic fusion, lateral ventricles enlargement and hypoplasia of brainstem and cerebellum, microcephaly and microencephaly. Axial hypotonia associated with increased appendicular tone and hyper-excitable tendon reflexes were noticed at birth. On the second day of life, she manifested focal motor seizures poorly responsive to intravenous diazepam and phenobarbital and partially responsive to intravenous midazolam. An EEG, at day 2, showed a suppression burst pattern with multifocal ictal discharges. Brain MRI, performed at 18 days of life, showed a large right ventricle diverticulum (Fig. 2C) that displaced the right hemisphere laterally and pushed downward the cerebellum, which appeared dysplastic. The olfactory bulbs were absent and the olfactory sulci were hypoplastic. The falx cerebri was present whereas there was a diffuse simplified gyral pattern with lack of aqueduct and third ventricle visualization (Fig. 2C). Array - Comparative Genomic Hybridization (Array-CGH) (100 kb) and analysis of the aristaless-related homeobox X-linked (*ARX*) gene were normal. Moreover, plasma levels of very long chain fatty acids (VLCFA), serum sialotrasferrin pattern and plasma 7-dehydrocholesterol were normal. Chest X-ray, echocardiogram, kidney and bladder ultrasound were also normal. Funduscopic exam revealed bilateral dragged disc and hyperplastic posterior primary vitreous. Her health conditions progressively deteriorated and she died, despite intensive supportive care, at the age of 6 months.

Both cases have been recently added to a recent report of a large Italian cohort of children with PDE.[6]

2.2. Review of the literature

We conducted a literature review in Pubmed (up to November 2017) with the four following search keys: 1) "*ALDH7A1*" OR "pyridoxine" OR "PDE" AND "neuroimaging"; 2) "*ALDH7A1*" OR "pyridoxine" OR "PDE" AND "case report"; 3) "*ALDH7A1*" OR "pyridoxine" OR "PDE" AND "MRI". Within the available articles, we manually searched for "MRI" and "neuroimaging", to identify brain findings described in the reports.

3. Results

Targeted genetic analysis was performed on the proband's DNA by NGS on a targeted panel for early onset epileptic encephalopathy which showed a homozygous novel missense mutation [c.1256C > T, p.Ser419Leu; chr 5q23.2; NM001202404] in the *ALDH7A1* gene. In silico predictors (SIFT, POlyPhen, Mutation Taster, Mutation assessor, InterVar) were concordant in defining the variant, which alters a highly conserved aminoacid residue (GERP 4.59), as damaging/likely pathogenic.

Pyridoxine supplementation and lysine-restricted diet led to complete seizure control and improved psychomotor development in the first months of life.

Both parents were tested and, as expected, found to be heterozygote for the mutation. We could retrieve a stored DNA sample extracted from peripheral blood of the proband's deceased older sister and were also able to document a condition of homozygosity for the familial mutation.

Noteworthy is also the history of the previous pregnancies of the mother: a female who died at 3 days of life, reasons not investigated; a pregnancy interrupted at 22 gestational weeks because of a severe brain malformation in the foetus; two spontaneous abortions (gestational weeks: unknown), two other normal pregnancies resulted in the birth of a healthy female (2008) and a healthy male (2011).

The proband was discharged from the hospital at 2 months of age with oral therapy with pyridoxine, levetiracetam, phenobarbital, arginine and lysine-restricted diet. At follow-up (age 18 months) clinical evaluation showed a global developmental delay: mild gross motor skills delay, cognitive impairment and moderate language delay. The last EEG, performed at 18 months of age, was normal and the antiepileptic therapy was then gradually suspended.

In order to better understand the possible association between brain MR abnormalities and *ALDH7A1* mutations, we conducted a literature review. A PubMed search for reported cases of *ALDH7A1* mutations associated with brain MR abnormalities yielded a total of 58 patients from 25 papers.[1,7–30] The neuroradiological findings of previously published cases and those of our cases are summarized in Tables 1 and 2.

The most frequently reported abnormalities (Tables 1 and 2) include the followings: agenesia/hypoplasia of corpus callosum (20/60, 33%), not specific white matter abnormalities (19/60, 32%), large cisterna magna (10/60, 17%), ventriculomegaly (10/60, 17%), haemorrhages (9/60, 15%), cerebellum hypoplasia/dysplasia (7/60, 12%), cortical atrophy (5/60, 8%), hydrocephalus (5/60, 8%), dysplasia of corpus callosum (4/60, 7%) and cysts (3/60, 5%). Other rare findings include basal ganglia abnormalities, mesial temporal sclerosis, incomplete myelination and hypoplasia of the brainstem (1/60, 2%).

4. Discussion

Our study describes the clinical and neuroradiological phenotype of a novel familial *ALDH7A1* mutation. The proband presented a classical PDE phenotype, which included both the neurological (epileptic encephalopathy with refractory seizures responsive to pyridoxine and normal brain MRI) and the systemic (feeding difficulties, coagulopathy, anemia, sepsis and hepatomegaly) features of the disease and carried a missense mutation of *ALDH7A1* gene. The same *ALDH7A1* genotype was found in the post-mortem DNA sample of the proband's sister (case 2). Interestingly, her foetal brain MRI, at

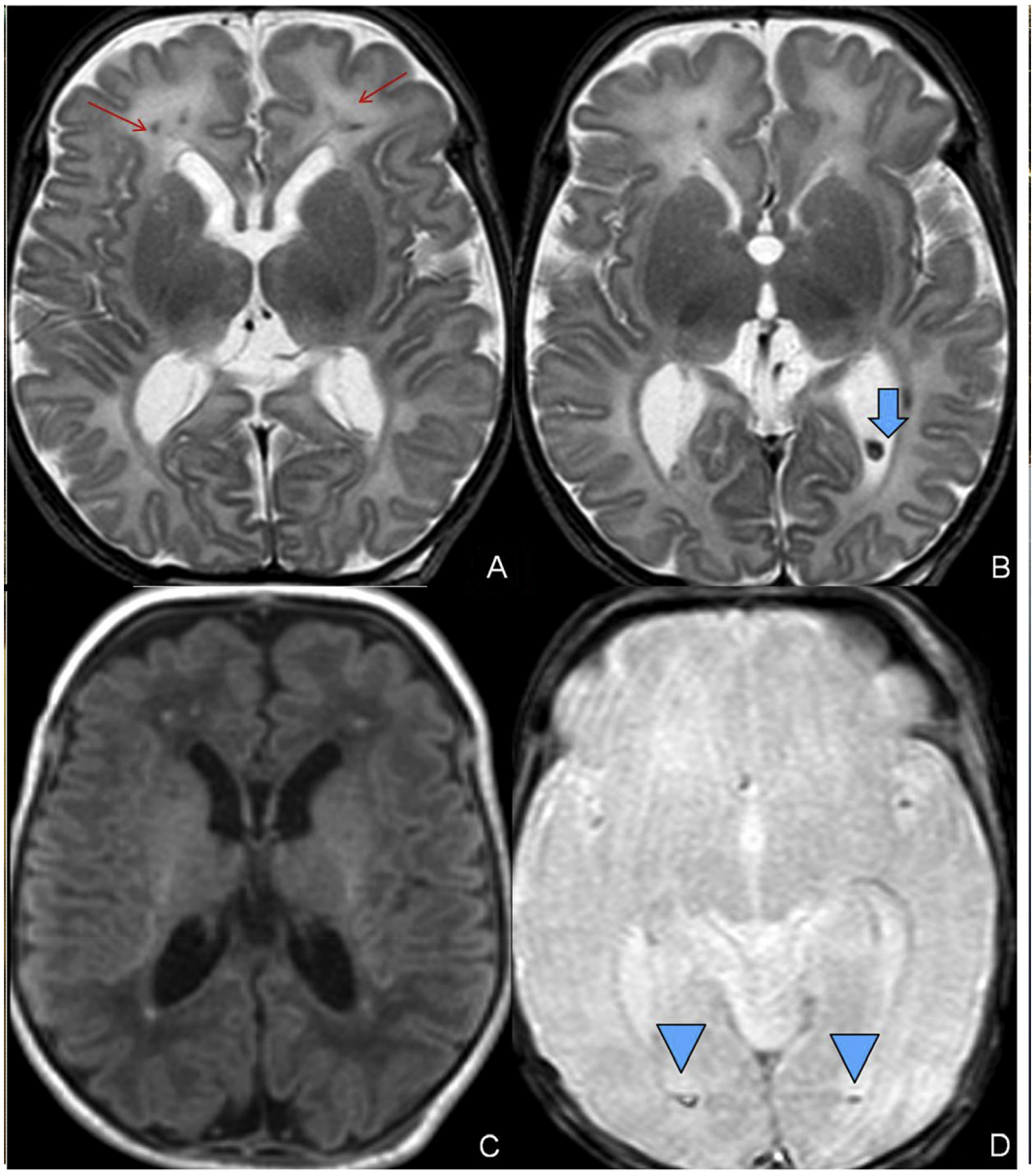

Fig. 1 – A-B) Axial T2-weighted images showing spotted white matter hypointensities (red arrows) compatible with minimal deep medullary vein thrombosis, note the corresponding axial T1 hyperintensity in C and focal left choroid plexus haemorrhage (blue arrow); D) axial Gradient Echo image showing tiny haemorrhagic spots in occipital horns of lateral ventricles. (For interpretation of the references to color/colour in this figure legend, the reader is referred to the Web version of this article.)

21 gestational weeks, documented a severe malformation with a striking involvement of the brainstem that likely led to acqueductal stenosis and ventriculomegaly and consequently to marked thinning of the cortical matter. The postnatal MRI confirmed these findings. As in the brother, she presented with neonatal refractory seizures and suppression burst activity on EEG. At the time, due to the diagnosis of epileptic encephalopathy symptomatic of a severe brain malformation, pyridoxine supplementation was not administered.

The mutation detected in the two siblings, never been reported so far, alters a highly conserved aminoacidic position and is predicted as pathogenic by the bioinformatic prediction tools. Related parents carried the mutation. All these data support the interpretation of this variant as disease-causing.

An alternative explanation for case 2 is a dual diagnosis, which may have been undetected, especially given the parental consanguinity and the high rate of miscarriages in the mother and the terminated pregnancy due to anencephaly. Probably whole exome sequencing could answer to this second hypothesis but unfortunately it is not feasible in case 2 due to deficient archival DNA.

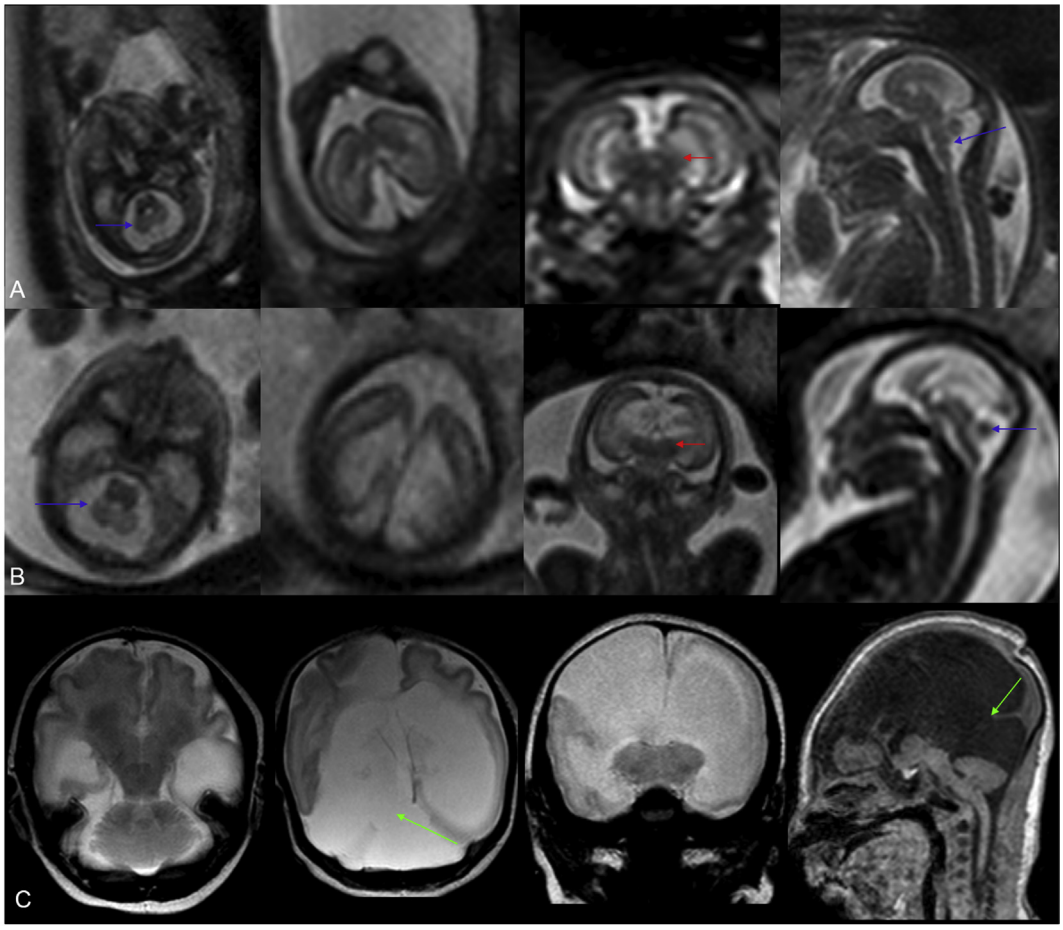

Fig. 2 – A-B) Axial, coronal and sagittal T2-weighted images at 21 gw of Case 2. Supratentorial structures are strikingly abnormal with apparent thalamic fusion (red arrow), severe lobar hypoplasia and microcephaly. Supratentorial ventricles are enlarged; cerebellum and brainstem hypoplastic (blue arrow). C) Postnatal MRI: brain findings have changed due to a large right ventricle diverticulum (green arrow), displacing the right hemisphere laterally and the cerebellum (which is dysplastic) downward; diffuse gyral simplification. (For interpretation of the references to color/colour in this figure legend, the reader is referred to the Web version of this article.)

From the literature review, we found that different brain abnormalities have been related to *ALDH7A1* gene defects (Tables 1 and 2) but their MRI pictures with a detailed description are available in few cases. To the best of our knowledge, no reports of foetal MRI in cases with *ALDH7A1* mutations have been reported so far.

As shown in Table 1, the occurrence and the type of brain malformations can vary in affected individuals of the same family. In fact, siblings carrying the same *ALDH7A1* pathogenic mutations often show different neuroradiological findings. Rankin et al.[15] reported three siblings (N. 4–6, Table 1) of whom one with borderline normal brain MRI, one with lack of white matter and the third one with lack of white matter associated to thinning of the corpus callosum. Bok et al., 2012[18] described two families in which two sets of siblings were either compound heterozygotes or homozygotes for *ALDH7A1* mutations (N. 10–11, Table 1): in the first family one sibling had a normal brain MRI, while the other showed ventriculomegaly and large cisterna magna; in the second family, one child showed an enlarged cisterna magna and the other one corpus callosum dysplasia and ventriculomegaly (N. 15–16, Table 1).

As mentioned above, some of the features presented by our patient (case 2) are very rare, in particular ventriculomegaly, which is reported only in 7 out of 60 cases. The leading alteration in our patient is the dysplasia of the brainstem which, to the best of our knowledge, has been involved in only one of the cases reported so far[1,15]; hydrocephalus is another very rare finding previously reported in less than 5 cases.

Even if different MRI abnormalities presented by the proband's sister have already been described,[2] our literature review (Tables 1 and 2) reveals that our case is far more complex and severe than the ones previously described.

In the literature, it is still unknown if brain abnormalities associated with *ALDH7A1* mutations have an effect on the electroclinical phenotype, given that most of these abnormalities do not involve the cerebral cortex, differently from other epileptogenic malformations.

Table 1 – Review of literature describing reported cases of *ALDH7A1* mutations associated with brain MRI abnormalities/malformations.

N.	Novel/reference	M/F	Mutation	Crisisonset	Starting B6	Neonatal MRI	Ageat F-up	F-up MRI	QI
1	Scharer 2010[9] Gallagher 2009[10] Kanno 2007[11]	M	c.248G > A + c.1208C > T	<7d	<7d	large cisterna magna and a small right parietal hemorrhage.	1y3mo	loss of white matter in parietal/ occipital lobes, thinning of posterior corpus callosum, increased T2 and FLAIR signal in frontal white matter, mega cisterna magna	NA
2	Jain-Ghai 2014[7]	M	c.446C > A + c.919C > T	7d	21d	bilateral asymmetric ventriculomegaly caused by bilateral subependymal cysts	5d	NA	NA
3	Salomons 2007[12] Mills 2010[13] Jansen 2014[14]	F	c.750G > A + c.505C > T	8d	3yrs	NA	13mo 20mo	normal porencephaly at the site of surgical resection, thinning of corpus callosum, gliosis in the periatrial region and posterior centrum semiovale, delay in myelination, bilateral high signal intensity in the hippocampus, prominence of cortical sulci.	NA
4	Rankin 2007[15] Mills 2006[1]	M1	Y380X + Y380X	4h	2mo	NA	7y3mo	mild global lack of white matter, thinning of posterior corpus callosum	44
5	Rankin 2007[15] Mills 2006[1]	M2	Y380X + Y380X	3h	antenatal (2–4 GW)	NA	5y8mo	hypoplasia of white matter (including corpus callosum, brainstem, cerebellum, pons)	54
6	Rankin 2007[15] Mills 2006[1]	M3	Y380X + Y380X	no	antenatal (2–4 GW)	NA	4y	borderline normal, minimal lack of white matter bulk	52
7	Nam 2012[16]	F	c.1279G > C + c.1279G > C	3d	9 mo	hyperintensity of basal ganglia	NA	NA	NA
8	Yeghiazaryan 2011[17]	F1	c.311+1G > A + c.311+1G > A	5h	10d	normal (on CT)	15y	slight diffuse cortical atrophy, thinned corpus callosum	40
9	Yeghiazaryan 2011[17]	M2	c.311+1G > A + c.311+1G > A	Birth	Birth	NA	13y	slight diffuse cortical atrophy	60
10	Bok 2012[18]	M1	c.1195G > C + c.1195G > C	no	antenatal	NA	12y	ventriculomegaly, enlarged cisterna magna	108
11	Bok 2012[18]	F2	c.1195G > C + c.1195G > C	1d	2,5mo	haemorrage	15y	normal	80
12	Bok 2012[18]	M1	c.1195G > C + c.1195G > C	no	antenatal	NA	3y	corpus callosum hypoplasia, white matter abnormalities on T2, ventriculomegaly	102
13	Bok 2012[18]	F2	c.1195G > C + c.1195G > C	Intrauterine	5d	corpus callosum hypoplasia, white matter abnormalities seen with diffusion MRI	5y	NA	73
14	Bok 2012[18]	F	c.1195G > C + c.1195G > C	1d	16d	white matter abnormalities seen with diffusion MRI	3,5y	white matter abnormalities on T2, ventriculomegaly	87
15	Bok 2012[18]	F1	c.1195G > C + c.1195G > C	2d	10d	NA	12y	white matter abnormalities on T2, enlarged cisterna magna	77

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Table 1 – (*continued*)

N.	Novel/reference	M/F	Mutation	Crisisonset	Starting B6	Neonatal MRI	Ageat F-up	F-up MRI	QI
16	Bok 2012[18]	F2	c.1195G > C + c.1195G > C	2d	3d	corpus callosum dysplasia, white matter abnormalities on T2	7y	corpus callosum dysplasia, white matter abnormalities on T2, ventriculomegaly	50
17	Bok 2012[18]	F	c.1195G > C + c.1195G > C	2d	5d	white matter abnormalities seen with diffusion MRI	2y6mo	cyst	63
18	Bok 2012[18]	M	c.1195G > C + c.1195G > C	2d	13d	white matter abnormalities seen with diffusion MRI, corpus callosum dysplasia, enlarged cisterna magna	2y6mo	corpus callosum hypoplasia, white matter abnormalities on T2	57
19	Bok 2012[18]	F	c.1195G > C + c.1195G > C	0d	3d	haemorrhage (on CT)	5y	corpus callosum dysplasia	55
20	Bok 2012[18]	F	c.1195G > C + c.1195G > C	1d	8mo	haemorrhage	5y	corpus callosum hypoplasia, ventriculomegaly	54
21	Bok 2012[18]	M	c.1195G > C + c.244C > T	1d	3d	normal	7y	corpus callosum hypoplasia, ventriculomegaly, mega cisterna magna	50
22	Oliveira 2012[19]	M	*c.505C>, p.(Pro169Ser) + c. 1217_I218delAT.p.(Tyr406CysfsX3)*	12h	12h	NA	9mo	atrophy with hypoplasia of corpus callosum	107
23	Oliveira 2012[19]	M	Homozygous deletion	1h	1d	NA	11y	thinning of posterior corpus callous	85
24	Bennett 2009[20]	M	c.1195G > C + c.1195G > C	<28d	1–2mo	hypoplasia of cerebellar vermis, cavum septum pellucidum, large posterior fossa cyst, hydrocephalus.	NA	NA	NA
25	Coci 2016[21]	M	c.566G > A + c.566G > A	3d	<28d	NA	9mo	hyperintense white matter in right cerebellar hemisphere, surrounded by edema	NA
26	Coughlin 2015[22]	F	c.448_458del11ntfsX45 + c.1195G > C	9d	11d	restricted diffusion scattered throughout the bilateral anterior and posterior periventricular white matter	25mo	white matter volume loss and gliosis, mild thinning of posterior corpus callosum	NA
27	Coughlin 2015[22]	F	p.G274E; p.S317L	13d	16d	mild diffuse cerebral swelling	NA	NA	NA
28	Coughlin 2015[22]	M1	p.P403L; ?	1w	1mo	hyperintensities within periventricular white matter on T2	18mo	hyperintensities on T2 in centrum semiovale and in frontal and parietal lobes	NA
29	Coughlin 2015[22]	M2	p.P403L; ?	1w	1mo	hyperintensities within periventricular white matter on T2	18mo	hyperintensities on T2 in the centrum semiovale and periventricular parietal white matter, focal dilatation of temporal horn of right lateral ventricle	NA
30	Coughlin 2015[22]	F	p.V278V; p.G398A	3d	5w	bilateral temporal lobe hemorrhages and thalamic changes	12y	bilateral mesial temporal sclerosis	NA
31	Mills 2010[13]	?	c.1482-1G > C + c.1482-1G > C	1h	?	diffuse signal and density abnormality of white matter in both cerebral hemispheres	NA	NA	NA

32	Mills 2006[1] Mills 2010[13]	M	c.1195G > C + c.611+5G > A	1h	4d	NA	?	agenesis corpus callosum, megacisterna magna, hydrocephalus	NA
33	Mills 2010[13]	?	c.446C > A + c.446C > A	14d	?	right frontal lobe focal brain abnormalities, cortical dysplasia, background of diffuse change, damage to lentiform nucleus	NA	NA	NA
34	Bennett 2009[20] Mills 2010[13]	?	c.1405+2T > C + c.1429G > C	4d	?	NA	?	atrophy of bifrontal/left temporal regions, hypoplasia of inferior vermis	NA
35	Mills 2006[1] Mills 2010[13]	?	c. 1195G > C + c.749delT	2d	?	NA	?	plexus bleeding both posterior ventricle horns, cystic lesions anterior horns	NA
36	Mills 2006[1] Mills 2010[13]	?	c.1195G > C + ?	6d	?	normal	10mo	cerebral atrophy of both hemispheres, poor myelination of cerebral hemispheres	NA
37	Mills 2010[13]	?	c.758delA + c.758delA	<1d	?	NA	?	agenesis of corpus callosum, neuronal heterotopias, cerebellar hypoplasia; subependymal grey matter heterotopia at temperal horn tips	NA
38	Plecko 2007[23] Gallagher 2009[10] Mills 2010[13]	?	c.248G > A + c.818A > T	7d	?	petechial haemorrhage in periventricular white matter, deep white matter lesions	4mo	long-standing hydrocephalus	NA
39	Mills 2006[1] Mills 2010[13]	M	c.434-1G > C + c.434-1G > C	12h	2d	NA	7mo	hydrocephalus	60–70
40	Mills 2006[1]	M1	c.228+2T > A + c.228+2T > A	<10m	7w	NA	?	megacisterna magna	NA
41	Mills 2006[1]	M2	c.228+2T > A + c.228+2T > A	<30m	1d	NA	?	megacisterna magna	NA
42	Mills 2006[1]	M	c.1512delG + c.1512delG	<1d	<1d	NA	?	vermis hypoplasia	79
43	Striano 2009[8]	M	c.433+5G > A + IVS5+5G > A	3h	<3d	megacisterna magna, cerebellar hypoplasia, ventricular dilation (on CT)	10mo	thinning of posterior corpus callosum, megacisterna magna, ventricular asymmetry, cerebellar hypoplasia, right subependymal heterotopia	88
44	Kanno 2007[11] Goto 2001[24]	M	IVS1+3A > T + P403L	2h	5mo	NA	?	moderate brain atrophy	NA
45	Baynes 2003[25]	M	NA	<1h	8h	NA	32y	thinning of posterior corpus callosum	71
46	Mercimek-Mahmutoglu 2012[26] Van Karnebeek 2012[27]	F	c.1192G > C + c.834G > A	4d	5d	bilateral hemorrhages temporal lobe and brain parenchyma; restricted diffusion ventral thalamic nuclei	2y4mo	evolution of intracranial hemorrhage and delayed myelination adjacent to occipital horns	NA
47	Gallagher 2009[10] Van Karnebeek 2012[27]	?	c.750G > A + c.1195G > C	2mo	2mo	NA	4y7mo	incomplete myelination adjacent to trigones bilaterally	NA
48	Van Karnebeek 2012[27]	?	c.872G > A + WT	<28d	5mo	NA	5mo	thinned corpus callosum, arachnoid cyst in the posterior fossa, wide extracerebral CSF spaces, myelination age-appropriate	NA

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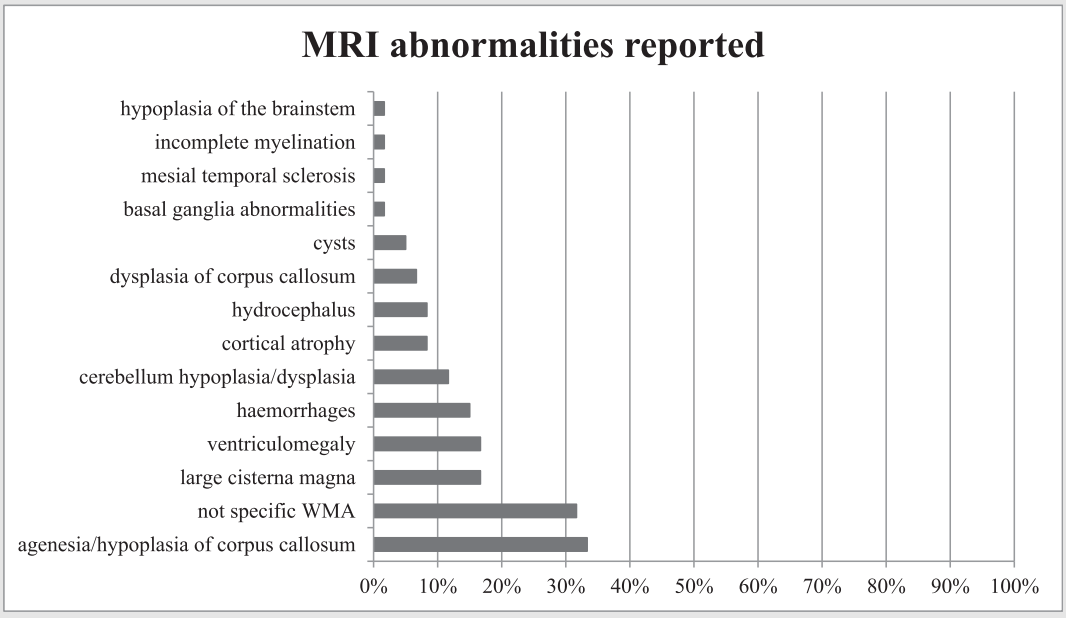
Table 1 – (*continued*)

N.	Novel/reference	M/F	Mutation	Crisisonset	Starting B6	Neonatal MRI	Ageat F-up	F-up MRI	QI
49	Van Karnebeek 2012[27]	?	c.1279G > C + c.1279G > C	<28d	2w	tiny periventricular and cerebellar hemorrhagic white matter injuries, subdural bleed, wide posterior fossa	3y	NA	70
50	Van Karnebeek 2012[27]	?	c.1279G > C + c.902A > T	<28d	6w	thinned splenium of corpus callosum, wide posterior fossa	11mo	thinned splenium of corpus callosum, normal MRS	NA
51	Van Karnebeek 2012[27]	?	c.427G > C + c.1344T > A	<28d	6w	thin corpus callosum	NA	NA	NA
52	Van Karnebeek 2012[27]	?	c.448_458del11 + c.1195G > C	<28d	2w	normal structure, but small areas of restricted diffusion in frontal white matter and thalami	NA	NA	NA
53	Bok 2010[28]	F1	c.1195G > C + c.1195G > C	1h	4d	bilateral lesions in the white matter on T2	5mo	thin corpus callosum and slight asymmetric ventriculomegaly	73
54	Bok 2010[28]	M2	c.1195G > C + c.1195G > C	no	antenatal	bilateral white matter abnormalities, thin genu corpus callosum	4y	bilateral white matter abnormalities, thin genu corpus callosum	98
55	Bok 2010[28]	F1	c.1195G > C + c.1195G > C	2h	10w	normal (on CT)	14y	normal	80
56	Bok 2010[28]	M2	c.1195G > C + c.1195G > C	7d	antenatal, restarted at 7th day	NA	12y	ventriculomegaly, enlarged cisterna magna	106
57	Ben Younes 2017[29]	F	c.393+1G > A + c.393+1G > A	0d	0d	NA	1y	decrease in volume of supratentorial white matter and thinning of the rostral corpus callosum	NA
58	Wang 2017[30]	M	NA	6mo	6mo	NA	6mo	right periventricular leukomalacia and gliosis	NA
59	Novel	F1	c.1256C > T + c.1256C > T	2d	no	large right ventricle diverticulum, hydrocephalus, dysplastic cerebellum, diffuse gyral simplification	NA	NA	NA
60	Novel	M2	c.1256C > T + c.1256C > T	3h	3d	few spotted white matter hypointensities on T2 weighted images, focal left choroid plexus hemorrhage, hemosiderin deposits in occipital horns of lateral ventricles	NA	NA	NA

CT: computed tomography, F: female, F-up: follow up, M: male, MRI: magnetic resonance imaging, NA: not available, IQ: intelligence quotient.

Table 2 – Synopsis of brain MRI abnormalities described in literature. MRI: magnetic resonance imaging; WMA: white matter abnormalities.



The association of brain malformations with *ALDH7A1* mutations should not be so surprising. In fact this gene encodes a protein, alpha-aminoadipic semialdehyde dehydrogenase, also called Antiquitin, which is expressed in early foetal life and plays a key role in the pipecolic acid pathway of lysine catabolism in brain. Interestingly, this protein is expressed both in radial glia and Bergmann glia and it is suggested to play a main role in neurogenesis and neuronal migration, during early foetal development.[14] Moreover, its expression in the choroid plexus and ependyma is thought to be involved in alteration of the CSF circulation of and may therefore contribute to ventriculomegaly and hydrocephalus.[14]

We believe the reported cases represent an interesting example of the association of brain malformations with *ALDH7A1* molecular defects and add to the current literature a novel evidence of a phenotype–genotype correlation, widening and strengthening the field of the *ALDH7A1* correlated defects.

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Conflict of interest

The authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ejpn.2018.06.010.

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