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Original article

Polymerase gamma deficiency (POLG): Clinical course in a child with a two stage evolution from infantile

myocerebrohepatopathy spectrum to an Alpers syndrome and neuropathological findings of Leigh’s encephalopathy

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## a r t i c l e i n f o

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## a b s t r a c t

*Aims:* Description of the clinical course in a child compound heterozygous for *POLG1* mutations, neuropathology findings and results of dietary treatment based on fasting avoidance and long chain triglycerides (LCT) restriction.

*Results:* At 31/2 months of age the patient presented with severe hypoglycemia, hyper- lactatemia, moderate ketosis and hepatic failure. Fasting hypoglycemia occurred 8 h after meals. The hypoglycemia did not respond to glucagon. She was supplemented with IV glucose and/or frequent feedings, but developed liver insufficiency which was reversed by long-chain triglyceride (LCT) restriction. Alpha-foeto-protein (AFP) levels were elevated and returned to low values after dietary treatment. Liver biopsy displayed cirrhosis, bile ductular proliferation, steatosis, isolated complex IV defect in part of the liver mitochon- dria, and mitochondrial DNA depletion (27% of control values). Two heterozygous muta- tions (p. [Ala467Thr] þ p. [Gly848Ser]) were found in the *POLG1* gene. At 3 years of age she progressively developed refractory mixed type seizures including a focal component and psychomotor regression which fulfilled the criteria of Alpers syndrome (AS) although the initial presentation was compatible with infantile myocerebrohepatopathy spectrum (MCHS). She died at 5 years of age of respiratory insufficiency. Neuropathologic

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investigation revealed lesions in the right striatal area and the inferior colliculi typical for Leigh’s encephalopathy.

*Conclusion:* The present patient showed an evolution from infantile MCHS to AS, and die- tary treatment seemed to slow the progression of liver failure. In spite of the late clinical features of AS, it extends the neuropathological spectrum of AS and polymerase gamma deficiency (POLG) to Leigh syndrome lesions.

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# Introduction

Mitochondrial DNA (mtDNA) depletionsyndromes(MDDS; MIM\* 251880), first described in 1991 by Moraes et al.[1](#_bookmark15) are heteroge- neous autosomal recessive disorders sharing marked reduction in mtDNA copy number in oneor more tissues. Generally, MDDS have an infantile or childhood onset with tissue specific features. The *POLG1* gene (MIM\*174763) is one of the several MDDS nuclear genes encoding proteins involved in the deoxy- ribonucleotide triphosphate metabolism and in mtDNA main- tenance. Early onset usually presents either an infantile myocerebrohepatopathy spectrum (MCHS) or Alpers Syndrome (AS).[2](#_bookmark16) An increasing number of *POLG1* mutations have been reported as a cause of AS.[2](#_bookmark16)e[11](#_bookmark16) Combined encephalopathy and liver failure with MDDS can also be due to mutations in other MDDS nuclear genes such as *PEO1* (*Twinkle*; MIM\* 60675), *DGUOK* (MIM\*601465), *MPV17* (MIM\* 256810) and *SUCLG1*[12](#_bookmark22) (MIM\* 245400).

In this paper, we report the clinical, biochemical, radiological

and neuropathological features of a 31/2 month-old patient with two different POLG mutations, who first met the diagnostic criteria for MCHS, subsequently for AS and then with Leigh syndromeneuropathologicalfeatures. Wecomparedtheclinical presentationwiththepresentationsofother MDDS nucleargene defects combining encephalopathy and liver failure and report the effects of dietary treatment onliver disease progression. The liver anatomopathological and enzymatic features of the present patient have been previously reported.[13](#_bookmark23)

# Case report

The present patient was born at term after an uneventful pregnancy from healthy non-consanguineous parents. Birth weight was 2970 g and length 50 cm. By the age of 31/2 months, following an overnight fasting with mild febrile illness, she presented with hypoglycemia, lactic acidosis, moderate ketosis and liver dysfunction. On admission, physical exami- nation was normal except a liver edge palpable at 3 cm below the right costal margin and a generalized hypotonia with preserved deep tendon reflexes. Weight was 4560 g (<P10), length 59 cm (P25) and head circumference 38.5 cm (<P10). She developed progressive jaundice and abdominal distension with ascites and increased liver echogenicity at ultrasound. Plasma amino acid chromatography showed increased alanine (1326 mmol/l: normal 128e441) level. Isoelectrofocus- ing of serum sialotransferrins was normal. Alpha-foeto- protein levels were increased from 311 to 3870.0 ng/ml (normal: 0e15.0 ng/ml). Urinary adipic acid (2025 mmol/g creatinine; normal: 30e440) and hydroxydicarboxylic acids

were increased. Urinary amino acids were normal. CSF anal- ysis showed slight increased protein (0.5 g/l; normal < 0.4 g/l) and lactate (2.92 mmol/l; normal 1.20e2.10) levels. [Table 1](#_bookmark11) shows laboratory data at different periods (at onset, after continuous IV glucose administration, nasogastric fractional meal supplemented with raw corn-starch, LCT and/or medium chain triglyceride (MCT) intake, following LCT restriction at days 55 and 63 after onset). Postprandial lactate was normal. In contrast, hypoglycemia and hyperlactacidemia were induced by fasting periods of 8 h and did not respond to IM glucagon. LCT restriction induced a decreased of abdominal distension and jaundice, associated with biochemical improvement of hepatocellular cytolysis and cholestasis. Later, alpha-foeto-protein levels also decreased to lower levels (35.2 ng/ml; normal: 0e15.0 ng/ml). At 18 months of age, she was able to walk by shuffling. She could speak approximately 20 words, combine two words together but not handle three word sentences. Few episodes of atypical absences followed by a drop attack were observed, but there was no psychomotor regression. Both EEG and brain MRI were normal. At the age of three years, her developmental quotient was 62 (Harvey test). A few months later she was admitted in status epilepticus with generalized tonico-clonic seizures. She had an intermit- tent tremor, moderate truncal ataxia with a wide-based gait. Between 4 and 49/12 years of age, she suffered 2 more episodes of status epilepticus requiring artificial ventilation and was treated with different anti-epileptic drugs except valproate. Developmental regression occurred with loss of walking ability and right-hand use. Additional seizure types appeared consisting of myoclonic seizures and epilepsia partialis con- tinua. EEG disclosed spike-wave complexes and paroxysmal delta and sharp waves predominantly in the right and left occipital area. Sensory conduction velocity (SCV) was decreased (left median nerve: wrist: 25.3 m/s (normal range 48.6 ± 3.0), left superficial peroneal nerve: not obtained). Late MRI disclosed on T2 sequence, a high signal abnormality in the right inferior colliculus as shown in [Fig. 1](#_bookmark12). At that time, the clinical diagnosis of AS was made, although the initial clinical feature was compatible with infantile MCHS. She died of respiratory insufficiency at the age of 5 years. Autopsy of both brain and medulla were performed.

# Investigations and results

The oxidation of 14C1-octanoate (14C1e8), 14C1-palmitate (14C1e16) and 14C1-succinate (14C1e4) in fibroblasts was normal. At the age of 8 months, a liver biopsy showed micro- nodular cirrhosis, with annular type fibrosis. Bile ductular

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| Table 1 e Laboratory features at onset, at days 5e9, at days 55 and 63, after continuous IV glucose infusion and/or fractional meal, continuous nocturnal nasogastric feeding, with MCT and LCT ingestion or LCT restriction. | | | | |
| Time | Onset | Days 5e9 | Day 55 | Day 63 |
| Lipid |  | LCT: 2 | LCT: | LCT: |
|  |  | MCT: 0.8 | MCT:1 | MCT:1 |
| Fractional meal þ raw corn-starch (5 g) |  | 4 h | 4 h | 4 h |
| Continuous nocturnal nasogastric feeding |  |  | þ (Day 45) | þ |
| IV glucose (10e30%) |  | þ |  |  |
| Glycaemia (4.16e6.10 mmol/l) a | (<0.5)a | 4.99 | 2.49 | 6.27 |
| Blood lactate (0.67e2.47 mmol/l) | 6.16 | 2.31 | 1.13 | 2.99 |
| Serum ASAT (<55 UI/l) | 244 | 1049 | 90 | 100 |
| Serum ALAT (<40 UI/l) | 273 | 483 | 40 | 47 |
| Serum bilirubin direct (<6.8 mmol/l) | 54.89 | 215.11 | 16.07 | 4.44 |
| indirect (<11.9 mmol/l) | 15.90 | 30.78 | 5.98 | 10.26 |
| LCT ¼ long-chain triglycerides (g/kg); MCT ¼ median-chain triglycerides (g/kg); a ¼ Dextrostix: mmol/l. | | | | |

proliferation was observed but no steatosis. Immuno-staining with a specific antibody against alpha-1 antitrypsin showed a normal pattern. Activities of fructose 1- phosphate aldolase (aldolase B), fructose-1, 6-biphosphatase and glucose-6- phosphatase in liver tissue were normal. At 17 months of age, histopathological analysis of a muscle biopsy was normal (including the absence of ragged red fibres) as well as OXPHOS activities. The results of the second liver biopsy have been reported elsewhere[13](#_bookmark23); most striking was a mosaic distribution of cytochrome oxidase activity as well as its immunolocalisa- tion in liver mitochondria. Blue native-Page of liver tissue showed a decreased activity of complex IV. The amount of mtDNA was 21% in muscle, 27% in liver and 98% in blood. Sequencing analysis of the deoxyguanosine kinase gene (*DGUOK* ) was normal. Mutation analysis of the POLG1 gene (blood cells) revealed two missense mutations: c.1399G>A

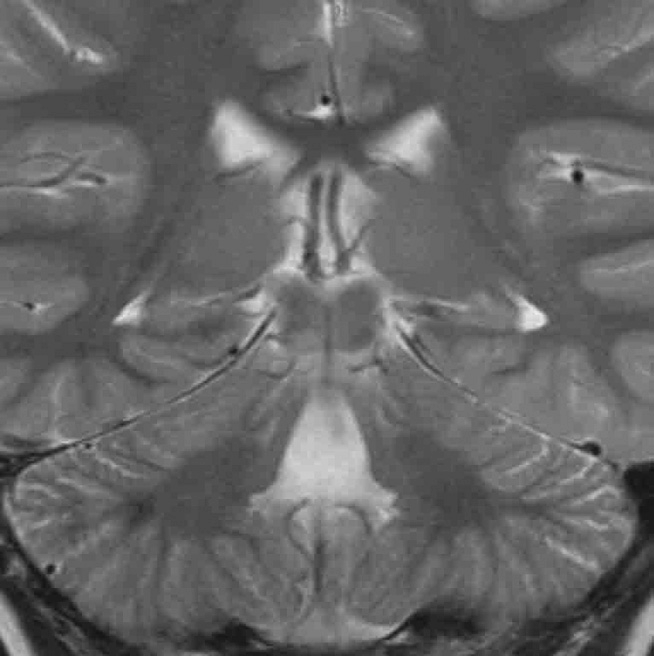


Fig. 1 e Late brain imaging performed at 410/12 years of age: coronal T2 image at the level of the inferior and superior colliculi shows abnormal increased signal intensity in the right inferior colliculus.

predicting p.Ala467Thr substitution (paternal) and c.2542G>A predicting p.Gly848Ser substitution (maternal).

Microscopic examination of the brain revealed a wide- spread cortical necrosis in the right striate cortex (primary visual cortex) associated with capillary endothelial cell swelling, congestion and spongiosis involving layer II and IV with relative preservation of neurons ([Fig. 2](#_bookmark13)A). Reactive (gemistocytic) astrocytes were observed in the middle and deep cortical layers. Astrogliosis was also present in the superior frontal, cingulate, parahippocampal, occipito- temporal gyri. In the neostriatum (caudate nucleus and putamen) neuronal cell dropout, chromatolysis, fibrillary gliosis, and pallor within the neuropil were visualized. The hippocampus was well preserved as well as the para- hippocampal gyrus. In the thalamus, only one area of the pars lateralis of the pulvinar showed a focal loss of large-size neurons associated with capillary endothelial cell swelling and congestion, vacuoles as well as astrogliosis. In the brainstem, the inferior colliculi displayed symmetric peculiar necrotizing lesions, capillary endothelial cell hypertrophy causing luminal narrowing and relative preservation of neurons with prominent Nissl endoplasmic reticulum ([Fig. 2](#_bookmark13)B). In the mesencephalic reticular formation and the pars compacta of the substantia nigra, there was only spon- giosis. The cerebellar cortex showed mild focal loss of Purkinje cells with pallor of the internal granular cell layer. The dentate nucleus showed neuronal depletion with vacuolization within the neuropil. In the spinal cord, myelin pallor, indicating fibre loss was observed in the posterior column as well as in the posterior spinocerebellar tract associated with mild astro- gliosis. Also Clarke’s column showed neuronal loss, but anterior horn neurons and intermediolateral cell columns seemed preserved.

# Discussion

At 31/2 months of age, the present patient presented an acute episode of fasting-induced hypoketotic hypoglycemia with hyperlactatemia and liver dysfunction. Plasma lactate reached its maximum levels when she was fasting and hypoglycemic as it can occur in gluconeogenesis disorders.[14](#_bookmark24) In the present case, glucose-6-phosphatase and fructose-1, 6-biphosphatase

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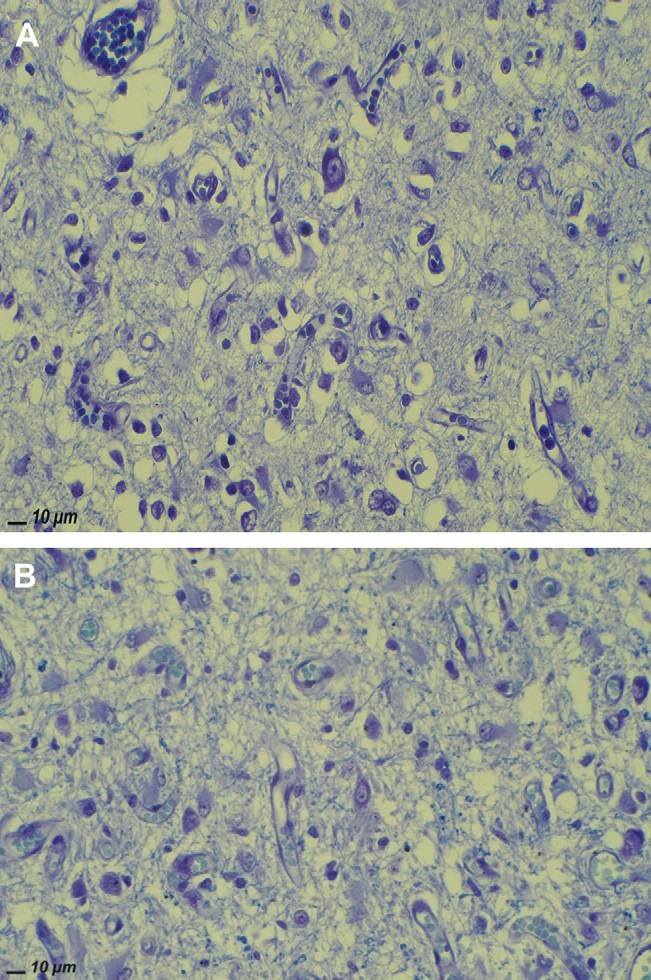


Fig. 2 e (A) Right area striata showing capillary endothelial cell swelling and congestion, astrocytic gliosis with

a conservation of neuronal perikarya. Paraffin embedding; Klu¨ ver-Barrera method. (B) Similar lesions in the inferior colliculi. Paraffin embedding; Klu¨ ver-Barrera method.

activities were normal. The clinical triad of MCHS defined by hypotonia, developmental delay and hepatopathy was found in the present patient. Additional diagnostic findings such as elevated CSF lactate were found, and later, at the age of 18 months, an onset of seizures and at 41/2 years a decreased SCV. Also, the characteristic features of the first liver biopsy per- formed at 91/2 months of age did not meet the criteria for the diagnosis of AS.[9](#_bookmark20) Of the 8 characteristic histological findings only micronodular cirrhosis and bile ductular proliferation were identified. Early dietary regimen initiated in the present patient with frequent nasogastric feeding and LCT restriction could have modified the fatty change like steatosis. Never- theless after the age of 41/2 years, the clinical triad of AS was present with refractory mixed type seizures including a focal component, psychomotor regression (episodic) and hepatop- athy with acute liver failure.[9](#_bookmark20) Three other additional clinical or laboratory features for AS were found including elevated CSF protein, abnormal EEG with asymmetric and high amplitude slow wave activity intermixed with polyspike discharges and liver enzymatic respiratory chain defects. In liver tissue, only complex IV showed a decreased activity suggesting that in this

case complex IV was the most vulnerable as seen in other MDDS.[10](#_bookmark21) The finding of normal muscle histochemical and OXPHOS activities emphasised the need to investigate several primary tissues as muscle analysis in the present case, gave misleading results. In the present patient under IV glucose and frequent feedings with LCT, we found a severe hepatic dysfunction including cytolysis, cholestatic jaundice, ascites like in long chain 3-hydroxyacyl CoA dehydrogensase (LCHAD), while MCT dietary fat had a beneficial effect. In LCHAD deficiency, liver cirrhotic changes are presumed to be a toxic effect of the accumulating 3-hydroxy fatty acids.[15](#_bookmark25) In the same way, in children harbouring POLG mutations, val- proic acid which is a branched chain carboxylic acid has been reported as very hepatotoxic in AS.[16](#_bookmark26) In some of the MDDS patients, an elevation of AFP levels can be a helpful diagnostic clue. In the present patient, AFP levels were initially markedly increased and subsequently returned to lower values (35.2 ng/ ml; normal: 0e15.0 ng/ml). Increased serum AFP level has been reported in *DGUOK* deficiency[17](#_bookmark27)e[20](#_bookmark27) and in *MVP17* deficiency.[21](#_bookmark29) The genotype of the present patient has been reported in AS. Most of AS affected patients carry the linker p.Ala467Thr mutation mostly associated with p.Trp748Ser another linker mutation or p.Gly848Ser mutation located in the polymerase domain.[2,5,6,22](#_bookmark16) In most patients with features of AS, the most prominent symptom is intractable progressive epilepsy, while hepatopathy develops later in the course of the disease. The *POLG1* gene (OMIM \*174763) is one of the nine MDDS nuclear genes. Six of them (*TK2*,[23,24](#_bookmark30) *RRM2B*,[25](#_bookmark31) *DGUOK*,[18](#_bookmark28) *SUCLG1*,

*SUCLA2*,[12,26,27](#_bookmark22) *TYMP*[28](#_bookmark32)) supply the mitochondria with nucleo-

tide pools needed for DNA replication. POLG[2](#_bookmark16) and Twinkle[29](#_bookmark33) products function directly at the mtDNA replication fork. *MPV17*[30](#_bookmark34) encodes an inner membrane mitochondrial protein of unknown function. Combined encephalopathy and liver failure can also be a feature of other MDDS nuclear genes such as Twinkle, DGUOK, MPV17 and SUCLG1 mutations. Patients with Twinkle mutation have liver insufficiency, major truncal hypotonia, seizures, peripheral sensitive neuropathy, growth retardation, abnormal eye movements and hyperlactatemia.[29](#_bookmark33) In DGUOK deficiency,[18](#_bookmark28) the majority of infants have chole- stasis, subsequently neurologic dysfunction with severe hypotonia, developmental regression and nystagmus, but no seizures or EEG abnormalities. In MPV17 defects, the patients are characterized by a variable neurological involvement at onset, absent or mild hyperlactatemia, consistently severe hypoglycaemia 3e4 h after meals, no hyperlactatemia after glucose loading, and beneficial effect of IV glucose and frequent feeding on liver function tests.[31](#_bookmark35) Mutations in *SUCLG1* were found in a patient with both Leigh disease and recurrent hepatic failure but also severe myopathy.[12](#_bookmark22)

[Table 2](#_bookmark14) emphasizes the neuropathologic microscopic

features of patients with AS or infantile hepatocerebral phenotype associated with POLG mutations in *POLG1* gene reported in the literature and those of the index patient har- bouring the p.Ala467Thr/p.Gly848Ser subtitutions.[2,3,5,7,32](#_bookmark16)e[34](#_bookmark16)

Although the late clinical features of the present patient corresponded to AS, she particularly exhibited lesions in the dorsal part of the mid brain and to a lesser extent in the deep grey structures and spinal cord, which were strikingly remi- niscent of those that occur in LS. Also, if the right calcarine lesion observed in the present patient belongs to the

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| Table 2 e Age of onset and death, presenting signs, neuropathologic features of patients with Alpers-Huttenlocher syndrome or infantile hepatocerebral phenotype associated with mutations (amino acid change) in POLG1 gene reported in the literature including the index patient. | | | | | | |
| Patient No | Sex | Age at onset/death | Presenting signs | Neuropathology: main microscopic features | POLG mutations (amino acid) | References |
| 2 | M | 5 m/13 m | Ep, En | Cx: >O, P, aF þ I (N, ND, NmC, p-G, VP, AC)a; | L244P/W748Sb | c [5](#_bookmark18),33 |
|  |  |  |  | Th þ IO: (ND, p-G); WM (p-d-G); Cl: |  |  |
|  |  |  |  | (s-PD, GLD, p-B, G); DN: (ND, G) |  |  |
| 1 | M | 7 y/19 y | GI, Ep, En | Cx: >O-st: (NmC, GA; s-ND, s-G, S, VP, AC); | A467T/A467T | d [5,34](#_bookmark18) |
|  |  |  |  | Cl þ IO þ SG (s-ND, p-G); DC: DE |  |  |
| 1 | M | 19 m/42 m | En | Cx: (m-A, py-pl-S, ND >II, III, V); | A467T/E873X/ E873X | [2,32](#_bookmark16) |
|  |  |  |  | O-st: (s-py-ND, G); Cl: (p-A, PD, sp-GL) |  |  |
| 2 | M | 15 m/21 m | En, Ep | Cx: >O (s-A, HE, G, ND, pl-N, S > III, V); | A467T/E873X/ E873X |  |
|  |  |  |  | Cl: (s-A, PD, G) |  |  |
| 3 | F | 1 y/6.5 y | Ep, PD, LF | Cx: >O (d-ND, G, S) | W748S/G848Sb | [3](#_bookmark17) |
| 2 | F | 4 m/8 m | GI, Ep | d-EM | W748Sb/Y1210fs1216X | [5](#_bookmark18) |
| 5 | M | 7 m/2.5 y | FT, PD, GI | Cm (S); Cl (f-IN); MTS | A467T/G848S |  |
| 1 | F | 12 m/4 y | Ep, En | Cx:wi >O (ND, S, G)a; sc-WM > O (G, S); | A467T/R574W | [7](#_bookmark19) |
|  |  |  |  | Hp-So (ND); Th (ND, G, S); GP (m-S)a; |  |  |
|  |  |  |  | Cl (s-PD, B, f-GLD); DN (ND, S) |  |  |
| 2 | F | 7 m/14 m | Ep, En | Cx: (p-ND, G, S,VP)a; sc-WM: (f-G); | A467T/R574W |  |
|  |  |  |  | BG þ Th: (ND, mS)a; MB: (ND, G, m-S, VP); |  |  |
|  |  |  |  | Cl: (s-PD, B, f-GLD) |  |  |
| 4 | F | 5 y/14 y | En, Ep | Cx: >O-sup-F (p-ND, s-G, S, VP)a; sc-WM | A467T/W748Sb |  |
|  |  |  |  | (G, m-S); Hp (RPN); Th (p-S, RPN); GPa þ |  |  |
|  |  |  |  | MB þ ME (m-S); Cl: (s-PD, B, f-p-GLD; GL þ |  |  |
|  |  |  |  | WM: m-S; DN (ND, S, G) |  |  |
| 7 | M | 6 m/13 m | PD, FT, Ep | Cx: nl; Cm: WM (p-G, m-S); Th (m-S, RPN); | M1163Rb |  |
|  |  |  |  | Hp-So (p-ND, G); Cl: (f-PD), DN: (p-ND, S), |  |  |
|  |  |  |  | WM: (f-S). |  |  |
| Index | F | 3.5/5ye | LF, PD | Cx: r-O-st (wi-N, RPN, S (II, IV), s-G, GA, e-VP); | A467T/G848S |  |
| Patient |  |  |  | Th: (RPN, m-S; Pul: f-ND, G, m-S, e-VP); nST: |  |  |
|  |  |  |  | (ND,G) Hp: Nl; IC: (sy-N, RPN, e-VP); Cl: (m-f-PD); |  |  |
|  |  |  |  | DN: (ND, m-S); Ck: (ND) |  |  |
| Clinical signs: Ep ¼ epilepsy, En ¼ encephalopathy; FT ¼ failure to thrive; GI ¼ gastro-intestinal problems; LF ¼ liver failure; PD ¼ psychomotor delay.  Neuropathology: A ¼ atrophy; AC ¼ anoxic changes of the neurons along with clusters of cells with fragmented apoptotic nuclei; B ¼ proliferation of Bergmann glia.  BG ¼ basal ganglia; Ck ¼ dorsal nucleus of Clark; Cl ¼ cerebellar cortex; Cm ¼ cerebrum; Cx ¼ cerebral cortex; DC: dorsal columns of the spinal cord; DE ¼ demyelination.  DN ¼ cerebellar dentate nucleus; EM ¼ encephalomalacia; (a) (sup) F ¼ (anterior) (superior) portions of the frontal lobes; (sp) GL ¼ (sparing of the) granular cell layer.  GLD ¼ granular cell layer dropout; G ¼ reactive gliosis; GA ¼ reactive (gemistroytic) astrocytes; GP ¼ globus pallidus; HE ¼ hydrocephalus ex vacuo.  Hp(So) ¼ hippocampus (especially in the Sommer sector); I ¼ insula; IC ¼ Inferior colliculi; IN ¼ infarcts; IO ¼ inferior olive nuclei; IIeIIIeV ¼ principally affecting layers IIeIII and V.  MB ¼ mammillary bodies; ME ¼ mesencephalon; MTS ¼ mesial temporal sclerosis; N ¼ necrotizing lesions; N (m) C ¼ neuropil (micro) cysts; ND ¼ neuronal dropout; nST ¼ neostriatum; O (st) ¼ occipital (striata area); P ¼ parietal; PD ¼ Purkinje cell dropout; Pul ¼ pulvinar; S ¼ spongiosis; RPN ¼ relative preservation of neurons; SG ¼ spinal sensory ganglia; Th ¼ thalamic nuclei; (sc) WM ¼ (subcortical) white matter in affected areas; (e) VP ¼ vascular proliferation (with endothelial hypertrophy).  Others: F ¼ female; M ¼ male; m ¼ months; Nl ¼ normal; r ¼ right; sy ¼ symmetric; y ¼ years, >: most prominent; d, f, m, p, py, pl, s, wi ¼ diffuse, focally, mild, prominent, patchy, cortical pseudolaminar, severe or widespread.   1. Astrocytes of Alzheimer type II. 2. Associated with the SNP 3428A/G (E1143G). 3. Ferrari, 2005 (patient s 4). 4. Ferrari, 2005 (patient s 8). 5. 2005. | | | | | | |

topography of AS, the relative preservation of neurons with capillary wall swelling is more typical of LS. In fact both Alpers and Leigh syndromes are characterized by prominent grey matter involvement, but each of these syndromes generally has different lesion topography and histological characteris- tics. In Leigh syndrome, lesions tend to be symmetrical and

predominate, as in the present patient, in the dorsal part of the brain stem, but also in the neostriatum, the cerebellar nuclei, the thalamus and the spinal cord.[35](#_bookmark36) However in both thalami and substantia nigra such lesions were not observed in the index patient but for the lateral part of the pulvinar. In contrast in AS, selective involvement of the calcarine cortex

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with patchy neuronal loss and gliosis is typical, although all cortical areas may be affected. White matter changes are usually slight in both AS and Leigh’s encephalopathy, but may predominate ([Table 2](#_bookmark14); reference [7](#_bookmark19), patient # 7). The lesions could correspond to energy imbalance in neurones or astro- cytes in areas incongruent to a vascular territory or sulcal topography.[36](#_bookmark37)

In conclusion, this case report particularly highlights the change from infantile MCHS to AS and the effects of dietary treatment in slowing the progression of liver failure. There- fore, we suggest to study the effect of LCT dietary restriction on liver function in other patients with AS or POLG associated hepatopathy. Finally, this report extends the neuropatholog- ical spectrum of AS to Leigh’s lesions.

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