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Metabolic Stroke in Carbamyl Phosphate Synthetase Deficiency

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Abstract

Stroke-like episodes with hemiparesis have been described in children with different inherited metabolic diseases. We report the novel observation of a severe stroke as the presenting sign in an 18-month-old girl with carbamyl phosphate synthetase (CPS) deficiency. MRI revealed infarction within the territory of the right middle cerebral artery. Localized ¹H-NMR spectroscopy showed elevation of glutamine (at 2.0–2.5 and 3.7 ppm) and lactate within the region of infarction. CPS activity in the liver was reduced (2.5 mU/mg protein, n = 12–35). On a protein-restricted diet including arginine supplementation, the child has developed well

with moderate mental retardation: no neurologic relapses have been observed over a period of 4 years.

CPS deficiency has to be added to the list of metabolic diseases that may lead to stroke-like episodes. In every case of unclear hemiparesis in childhood, urea cycle defects should be included in the differential diagnosis.

Key words: Stroke – Urea cycle defect – Carbamyl phosphate synthetase

Abbreviations:

CPS: carbamyl phosphate synthetase
OTC: ornithine transcarbamylase
MRI: magnetic resonance imaging
¹H-NMR: proton nuclear magnetic resonance
MELAS: mitochondrial encephalopathy, lactic acidosis, stroke-like episodes
HSE: herpes simplex encephalitis
NAA: n-acetyl aspartate
CDG: carbohydrate-deficient glycoprotein

Introduction

Stroke-like episodes with hemiparesis and reversible or irreversible brain damage have been described in an increasing number of different inherited metabolic diseases which have been reviewed recently (25, 26, 28, 35, 41) (Table 1). The pathogenetic mechanisms of stroke in these metabolic disorders are heterogeneous and often remain unclear. Endothelial wall damage, platelet dysfunction, coagulation disturbances, perfusion abnormalities and accumulation of toxic metabolites have been considered as possible explanations for the neuronal dysfunction (20).

Several patients with urea cycle defects and stroke-like episodes as the presenting symptom have been described. These cases include hemizygotic (7) and heterozygotic children (11) with ornithine transcarbamylase (OTC) deficiency and acute symptoms of hemiplegia (7, 9, 11, 31).

We report on an 18-months-old girl with recurrent episodes of hemiparesis, hyperammonemia and mild lactic acidosis who had

Table 1 Inherited metabolic diseases with stroke:

A. Organic acidurias
Homocystinuria (4, 8), propionic-(10), methylmalonic-(40), isovaleric acidemia (14), glutaric aciduria type I (1, 17, 18, 27), glutaric aciduria type II (41), 3-methylcrotonyl-CoA carboxylase deficiency (38), 3-hydroxy-3-methylglutaryl-coenzyme A lyase deficiency (23)
B. Mitochondriopathies
Mitochondrial myopathies (5), Leigh disease (33), MELAS syndrome (34), COX deficiency (30)
C. Lysosomal storage disorders
Fabry disease (19), cystinosis (42)
D. Urea cycle defects
OTC deficiency (7, 11), CPS deficiency (this report).
E. Other
Sulfite oxidase deficiency (37), hyperlipoproteinemia (16), CDG syndrome (3), phosphoglycerate kinase deficiency (39)

suffered infarction of the right middle cerebral artery territory. Elevated glutamine and lactate levels were detectable by ¹H-NMR-spectroscopy in the infarcted area. Enzymatic measurement of a liver specimen finally revealed CPS deficiency.

Case report

This girl was the fourth child of non-consanguineous Caucasian parents. Pregnancy, labour and the postnatal period were uneventful. Her oldest sister suffered from cystic fibrosis. The remaining family history was unremarkable. At the age of 17 months, the patient was first admitted to a local hospital because of an episode of apyretic somnolence. Psychomotor development had been moderately retarded, walking was possible with help, and muscular hypotonia had been observed. Herpes simplex encephalitis (HSE) was suspected and treatment with acyclovir was started. Investigation of laboratory parameters, including cerebrospinal fluid, revealed nothing abnormal. After 4 days, the girl was transferred to our hospital. She recovered neurologically

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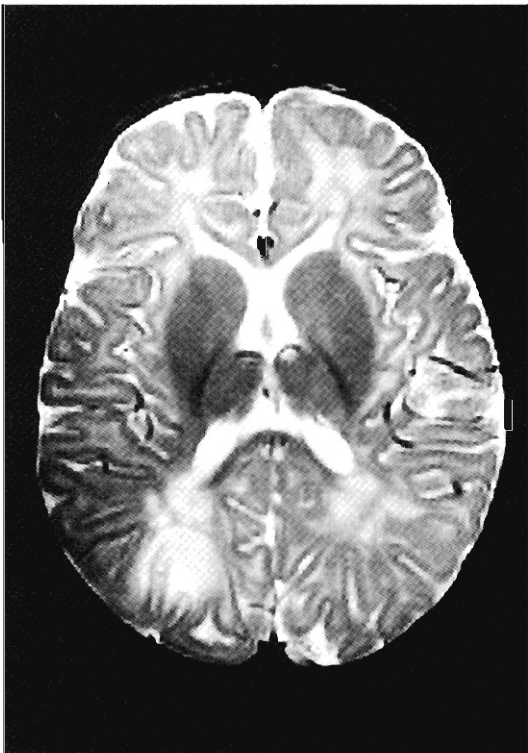


Fig. 1 The T_2 -weighted image (TR = 2400 ms, TE = 90 ms) at the first presentation of the patient showed bilateral hyperintensities within the white matter and a focal signal-intense lesion in the border zone between the territories of the middle cerebral artery and the posterior cerebral artery.

within a few days without the need for other treatment. Further laboratory investigations revealed only moderate, transient elevations of lactate (2.2 mmol/l, $n = < 1.8$ mmol/l) and ammonia (117 μ mol/l, $n = < 50$ μ mol/l). On MRI, first abnormalities were observed (Fig. 1), characterized by abnormally high-signal intensities around the periventricular white matter.

One month later, after a two-day upper respiratory tract infection, the child was readmitted because of progressive left-sided hemiparesis and repeated vomiting. During the hospital stay, the hemiparesis worsened and generalized ataxia developed. On the third day, the girl experienced a sudden crisis with somnolence and focal convulsions of the left extremities. MRI showed an abnormal, hyperintense signal confined to the entire territory of the right middle cerebral artery (Fig. 2a). Doppler and Duplex sonography and transfemoral angiography were normal. Clotting disorders, including protein C and S deficiencies, were excluded. Laboratory data during the crisis revealed hyperammonemia (688 μ mol/l) and elevations of lactate (3.6 mmol/l) and pyruvate (0.146 mmol/l, $n < 0.064$ mmol/l) in blood. Lactate in CSF was 3.6 mmol/l ($n = < 2$ mmol/l). Blood cell count, blood gas analysis, transaminases, coagulation parameters, glucose, and all serological parameters for viral infections in plasma and CSF were normal.

Plasma amino acid analysis revealed elevations of glutamine (938 μ mol/l, $n: 20$ –600 μ mol/l), alanine (1014 μ mol/l, $n: 99$ –350 μ mol/l), α -aminobutyric acid (131 μ mol/l, $n: 0$ –25 μ mol/l) and lysine (369 μ mol/l, $n: 45$ –144 μ mol/l). Citrulline was 26 μ mol/l ($n: 5$ –24 μ mol/l). In the course of the disease, glutamine levels increased to 1008 μ mol/l and alanine decreased to 458 μ mol/l as well as did lactate and pyruvate. GC/MS analysis of urine for

organic acids did not reveal any abnormalities. Follow-up of plasma amino acids over a period of 4 years showed glutamine levels remaining high (700–900 μ mol/l), alanine becoming normal, although in the upper normal range, and citrulline falling below the limit of detection. An allopurinol loading test was normal. Total plasma carnitine was 30 μ mol/l ($n = 34$ –52 μ mol/l), acyl-carnitine 4 μ mol/l ($n = 1$ –7 μ mol/l). Muscle biopsy revealed a slightly increased lipid content but mitochondrial structure was normal on histologic examination. Mitochondrial DNA analysis for the known MELAS point mutations revealed no abnormalities.

Dexamethasone and mannitol were given for brain edema during the acute episode. Because of the unexplicable hyperammonemia, a low-protein diet (1 g/kg b.w./day) supplemented with UCD 2 (Milupa) and L-carnitine (100 mg/kg b.w./day) was started. The child recovered within a few days and remained neurologically stable thereafter. The hemiparesis of the left arm improved significantly and the ataxia resolved. No neurological decompensation occurred over a period of 4 years. The child, now 6 years old, shows mild mental retardation (developmental score, Kaufman Assessment Battery for Children, SED 65, SGD 80, SIF 74, estimated IQ 80–85). A needle liver biopsy was performed to measure urea cycle enzymes. The sample was frozen immediately in liquid nitrogen and sent to Berne on dry ice.

Methods

Magnetic resonance imaging (MRI) and NMR spectroscopy

MRI and NMR spectroscopy were performed on a 1.5 Tesla imaging/spectroscopy system (Siemens, Erlangen, Germany) using a circular polarized head coil. For imaging, T_1 -weighted (TR = 550 ms, TE = 15 ms, 4 mm slice thickness) and T_2 -weighted images (TR = 2400 ms, TE = 15/90 ms, 5 mm slice thickness) were acquired. For spectroscopy, we employed a stimulated echo sequence (12, 15). Localized spectra were acquired after optimization of the local magnetic field and of the chemical shift selective water suppression pulse from cubic volumes of interest (2.5 x 2.5 x 2.5 cm) using a TR of 1500 ms and a TE of 270 ms. In total, 382 excitations were accumulated, resulting in an examination time of 9 minutes for a local spectrum. Spectra were corrected for eddy currents using an unsaturated localized H_2O spectrum and 1st order phase correction.

Enzyme assays

Liver (10–20 mg) was homogenized in the 50-fold volume (0.5–1 ml) of ice-cold water. CPS activity was determined spectrophotometrically by following the synthesis of citrulline from ammonia, bicarbonate and ATP in the presence of ornithine and ornithine transcarbamylase. The assay mixture contained in a total volume of 0.35 ml 33 μ mol NH_4HCO_3 , 6 μ mol ATP, 3 μ mol N-acetyl-glutamate, 2 μ mol ornithine, 5 μ mol $MgSO_4$, 25 μ l CPS-free ornithine transcarbamylase (Mc Lean et al) (32) and 50 μ l liver homogenate. After five minutes pre-incubation in the absence of the liver homogenate, citrulline formation was allowed to proceed for 15 min at 37°C. The reaction was stopped by the addition of 0.25 ml of 0.5% tungstophosphoric acid in 5% trichloroacetic acid. After centrifugation, citrulline was determined in the supernatant by the diacetyl-monoxime-antipyrine reaction according to Ceriotti and Spandrio (6) using synthetic citrulline as a standard.



Fig. 2a

OTC activity was determined in the same manner by following citrulline synthesis from L-ornithine (2.5 mM) and carbamyl phosphate (5 mM) in triethanolamine/HCl (270 mM, pH 7.7). One unit of CPS or OTC activity is defined as the amount of enzyme producing 1 μ mol citrulline per minute. Protein was determined by the method of Lowry (29) using bovine serum albumin as standard.

Results

MRI and NMR spectroscopy findings

At the first presentation (Fig. 1) the T₂-weighted image showed bilateral abnormal high signal intensity of the white matter around the frontal horns and the posterior horns of the lateral ventricles. In addition, there was a signal intense lesion extending from the right posterior horn of the lateral ventricle into the subcortical white matter.

One month later, after onset of the left-sided hemiparesis MRI showed infarction of the entire right middle cerebral artery territory (Fig. 2a). Localized ¹H-NMR of the affected hemisphere (Fig. 2b) yielded a marked increase in cerebral lactate, consistent with ischemic infarction. In addition, there were signals between 2 and 2.5 ppm as well as 3.7 ppm, that could be attributed to elevated glutamine levels according to Connelly et al (9). In the contralateral hemisphere, there was a resonance at 3.7 ppm that also suggested some elevation of glutamine (Fig. 2c).

Two months later, atrophy of the infarcted hemisphere had developed and the right lateral ventricle dilatated. The proton NMR spectra at that time revealed no elevation of glutamine. In the region of the infarct, NAA was decreased. Lactate was still elevated.

right hemisphere

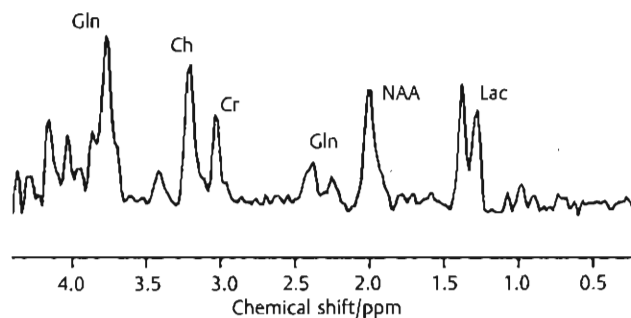


Fig. 2b

left hemisphere

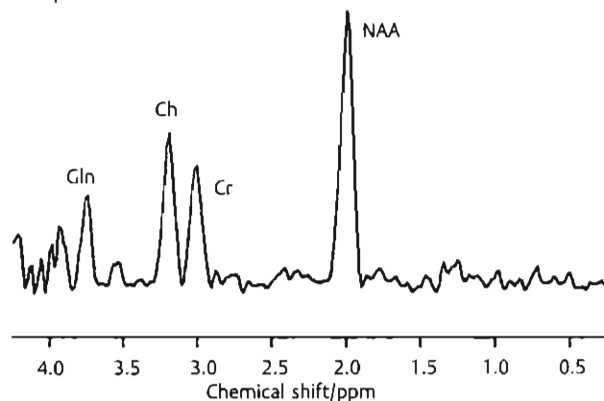


Fig. 2c

Fig. 2a to c After acute onset of left-sided hemiparesis the T₂-weighted image (same parameters as Fig. 1) at the level of the basal ganglia shows abnormal signal intensity within the entire territory of the right middle cerebral artery (a). Localized ¹H-NMR spectroscopy of 15.6 ml volumes of interest (2.5 × 2.5 × 2.5 cm VOI) was performed from the affected and the contralateral hemisphere. The localized spectrum of the affected hemisphere (TR = 1500 ms, TE = 270 ms 382 NEX) (b) yielded a marked increase in cerebral lactate. In addition, there were signals between 2 and 2.5 ppm as well as 3.7 ppm, that indicated elevated glutamine levels. In the contralateral hemisphere (c), there was a resonance at 3.7 ppm that also suggested elevation of glutamine.

One year later (Fig. 3a, b) the T₂-weighted images were unchanged, a partial resolution of the periventricular signal abnormalities was found (see also Figs. 1 and 2). The proton spectrum of the infarcted area yielded still elevated lactate at 3.7 ppm, glutamine was elevated to some extent. The spectrum of the normal hemisphere showed a normal relationship between NAA, choline and creatine.

The follow-up MRI three years later was unchanged. The proton spectra showed reduced NAA and choline/creatine, but no indication of lactate and glutamine in the right hemisphere. The proton NMR spectrum of the left hemisphere was normal.

Enzymatic findings

CPS activity was reduced in a liver biopsy with a residual activity of 2.5 mU/mg protein (normal = 12–35). OTC activity was in the normal range (338 mU/mg protein; normal = 160–560).

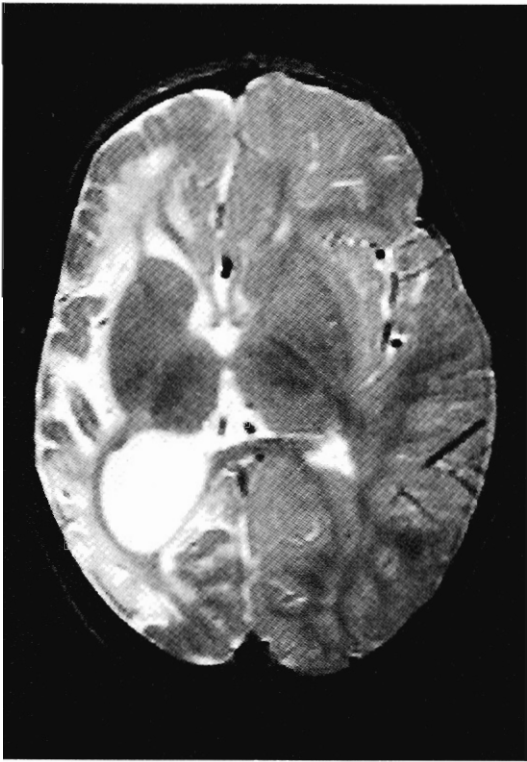


Fig. 3a

right hemisphere

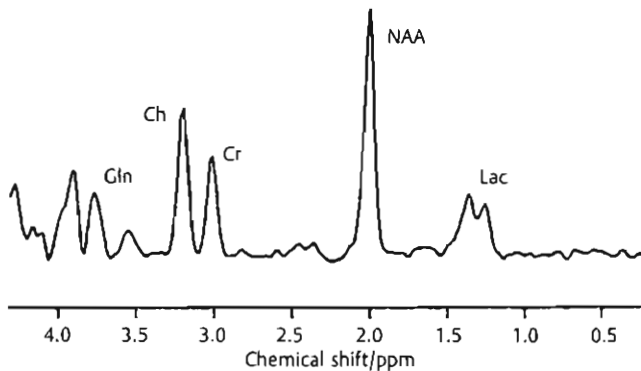


Fig. 3b

Fig. 3a and b One year later, the T₂-weighted (same parameters as in Figs. 1 and 2) images (a) revealed atrophy of the infarcted hemisphere and dilatation of the right lateral ventricle. The periventricular signal abnormalities showed partial resolution (see also Figs. 1 and 2). The proton spectrum (for parameters see Figs. 1 and 2) of the normal hemisphere revealed a normal relationship between NAA, choline and creatine. In the infarcted area on the right (b), lactate was still elevated and glutamine (3.7 ppm) was still elevated to some extent.

Discussion

We report on the novel observation of a severe metabolic stroke in the right middle cerebral artery territory in an 18-month-old girl with carbamyl phosphate synthetase deficiency. The initial clinical symptoms mimicked a cerebrovascular insult. MRI findings first suggested MELAS syndrome (24). Lactate, pyruvate and plasma alanine levels were moderately elevated. Moreover,

an elevation of lactate was also observed in ¹H-NMR spectroscopy. However, high levels of ammonia (approx. 700 μmol/l) in plasma during the crisis, constantly elevated levels of glutamine and rapid normalization of lactate levels thereafter did not fit into the clinical picture of MELAS syndrome. Muscle biopsy excluded all known point mutations of MELAS. Signals between 2 and 2.5 as well as 3.7 ppm in ¹H-NMR spectroscopy could be attributable to elevated glutamine. A similar finding was reported recently for a patient with OTC deficiency by Connelly et al (9). Therefore, a urea cycle defect, most probably OTC deficiency, was suspected as the underlying disease in our patient. However, urine analysis of organic acids showed no orotic aciduria and the allopurinol loading test was also normal. Other urea cycle defects except CPS and NAGS deficiency were ruled out on the basis of the plasma amino acid pattern. Finally, enzyme measurement in a liver biopsy specimen revealed CPS deficiency with a considerable residual activity.

Mitochondrial carbamyl phosphate synthetase (CPS I) (EC 6.3.4.16), the first enzyme in ureagenesis, is located in the mitochondrial matrix compartment and is expressed in liver and epithelial cells of intestinal mucosa. Two distinct clinical patterns result from autosomal recessively inherited CPS I deficiency: a lethal neonatal type with a complete or virtually complete deficiency of CPS I, and a late-onset type with partial enzyme deficiency. Recently, a mutation has been elucidated for the first time in a patient with a lethal course. A one-base substitution in an exon of the CPS I gene caused a 9 bp deletion in the mRNA due to aberrant splicing (22).

In our patient, the onset of the disorder was delayed and the clinical course was in accordance with the relatively high residual activity in liver tissue. Hyperammonemia and subsequent stroke may have developed as a consequence of catabolic stress during infection.

The pathophysiological mechanism that causes cerebral infarction in urea cycle defects remains unclear. Elevated levels of ammonia or a lack of arginine have been considered responsible for neurological deficits (28). Possible mechanisms resulting in encephalopathy may be altered energy metabolism, neurotransmitter imbalance, astrocyte swelling, changes in cerebral blood flow and intracranial pressure. Many of these phenomena could also be secondary to intracerebral glutamine accumulation (9, 13, 31).

It is unclear why different metabolic disorders can lead to a similar neurological pattern of stroke-like episodes. One explanation might be that all of them affect mitochondrial metabolism as well at the levels of the neurons or endothelial cells or smooth muscular cells of arterial walls (11). A current concept for MELAS suggests an imbalance between energy requirements and availability (21).

In methylmalonic acidemia, a combination of hypovolemia, acidemia and accumulation of organic acids may be a possible cause of a severe local deficit in energy metabolism (20, 40). Strokes might thus result from an acute, relative deficiency of cellular ATP. Focal seizure activity could also play an important role as a harbinger to stroke-like episodes. A focal seizure places extreme metabolic demand on brain tissue and may cause reversible or irreversible metabolic exhaustion of the epileptic zone.

Lactate elevation in our patient was most probably secondary, as it has also been observed in a patient with OTC deficiency, described by de Grauw et al (11), who had moderate lactate

elevation in plasma and CSF. In our patient, the stroke occurred predominantly in the right middle cerebral artery territory, but there was also bilateral involvement of the deep white matter. This suggests metabolic distress of brain tissue in addition to vascular damage leading to underperfusion. Similar clinical reports have been made for children with OTC deficiency (7, 9, 11, 31). *Batshaw* et al also described focal deficits in a patient with CPS deficiency (2).

In conclusion, it is important to be aware that acute hemiparesis in childhood mimicking a cerebrovascular insult may be due to a metabolic disturbance. We recommend to exclude urea cycle defects including OTC and CPS deficiency in all unknown causes of stroke or stroke-like episodes. These very rare urea cycle defects can easily be overlooked in selective screening, since only unspecific glutamine and alanine elevation is observed in the amino acid profiles and no organic aciduria is detectable.

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References

- Aicardi, J., F. Goutières, J. M. Saudubray, H. Ogier:* CT scans of infants with glutaric aciduria. *Dev. Med. Child Neurol.* 27 (1985) 403–404
- Batshaw, M., S. Brusilow, M. Walser:* Treatment of carbamyl phosphate synthetase deficiency with keto analogues of essential amino acids. *N. Engl. J. Med.* 292 (1975) 1085–1090
- Blennow, G., J. Jaeken, L. M. Wiklund:* Neurological findings in the carbohydrate-deficient glycoprotein syndrome. *Acta Paediatr. Scand. Suppl.* 375 (1991) 14–20
- Boers, G. H. J., A. G. H. Smals, F. J. M. Trijbels, B. Fowler, J. A. J. M. Bakkeren, H. C. Schoonderwaldt et al:* Heterozygosity for homocystinuria in premature peripheral and cerebral occlusive arterial disease. *N. Engl. J. Med.* 313 (1985) 709–715
- Bogousslavsky, J., E. Perentes, J. P. Deruaz, F. Regli:* Mitochondrial myopathy and cardiomyopathy with neurodegenerative features and multiple brain infarcts. *J. Neurol. Sci.* 55 (1982) 351–357
- Ceriotti, G., L. A. Spandrio:* Spectrophotometric assay for the determination of urea. *Clin. Chim. Acta* 8 (1963) 295–299
- Christodoulou, J., I. A. Qureshi, R. R. McInnes, J. T. R. Clarke:* Ornithine transcarbamylase deficiency presenting with stroke like episodes. *J. Pediatr.* 122 (1993) 423–425
- Clarke, R., L. Dlay, K. Robinson, E. Naughten, S. Cahalane, B. Fowler et al:* Hyperhomocysteinemia: an independent risk factor for vascular disease. *N. Engl. J. Med.* 324 (1991) 1149–1155
- Connelly, A., J. H. Cross, D. G. Gadian, J. Y. Hunter, F. J. Kirkham, J. Y. Leonard:* Magnetic resonance spectroscopy shows increased brain glutamine in ornithine carbamoyl transferase deficiency. *Pediatr. Res.* 33 (1993) 77–81
- Dave, P., R. G. Curless, L. Steinman:* Cerebellar hemorrhage complicating methylmalonic and propionic acidemia. *Arch. Neurol.* 41 (1984) 1293–1296
- DeGrauw, T. J., L. M. E. Smit, M. Brockstedt, Y. Meijer, J. v. d. Klei-v. Moorsel, C. Jakobs:* Acute hemiparesis as the presenting sign in a heterozygote for ornithine transcarbamylase deficiency. *Neuropediatrics* 21 (1990) 133–135
- Felber, S. R., W. Sperl, A. Chemelli, Ch. Murr, U. Wendel:* Maple syrup urine disease: metabolic decompensation monitored by proton magnetic resonance imaging and spectroscopy. *Ann. Neurol.* 33 (1993) 396–401
- Filloux, F., J. J. Townsend, C. Leonard:* Ornithine transcarbamylase deficiency: neuropathologic changes acquired in utero. *J. Pediatr.* 108 (1986) 942
- Fischer, A. Q., V. R. Challa, B. K. Burton, W. T. McLean:* Cerebellar hemorrhage complicating isovaleric acidemia: a case report. *Neurology* 31 (1981) 746–748
- Frahm, J., H. Bruhn, M. L. Gyngell, K. D. Merboldt, W. Hänicke, R. Sauter:* Localized high resolution proton NMR spectroscopy using stimulated echoes: Initial applications to the human brain in vivo. *Magn. Reson. Med.* 9 (1989) 79–93
- Glueck, C. J., S. R. Daniels, S. Bates, C. Benton, T. Tracy, J. L. H. C. Third:* Pediatric victims of unexplained stroke and their families: familial lipid and lipoprotein abnormalities. *Pediatrics* 69 (1982) 308–316
- Goodman, S. I., M. D. Norenberg:* Glutaric acidemia as a cause of striatal necrosis in childhood. *Ann. Neurol.* 13 (1983) 582–583
- Goodman, S. I., M. D. Norenberg, R. H. Shikes, D. Breslich, P. G. Moe:* Glutaric aciduria: biochemical and morphologic considerations. *J. Pediatr.* 90 (1977) 746–750
- Greuel, R. P.:* Stroke in Fabry's disease. *J. Neurol.* 241 (1994) 153–156
- Heidenreich, R., M. Natowicz, B. E. Hainline, P. Berman, R. I. Kelley, R. E. Hillman, G. T. Berry:* Acute extrapyramidal syndrome in methylmalonic acidemia: „Metabolic stroke“ involving the globus pallidus. *J. Pediatr.* 113 (1988) 1022–1027
- Hirano, M., S. G. Pavlakis:* Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke like episodes (MELAS): current concepts. *J. Child Neurol.* 9 (1994) 4–13
- Hoshida, R., T. Matsuura, Y. Haraguchi, F. Endo, M. Yoshinaga, I. Matsuda:* Carbamyl phosphate synthetase I deficiency. One base substitution in an exon of the CPS I gene causes a 9-base pair deletion due to aberrant splicing. *J. Clin. Invest.* 91 (1993) 1884–1887
- Huemer, M., A. Mühl, K. Wandl-Vergesslich, W. Strobl, S. Stöckler-Ipsiroglu:* Metabolic stroke in a child with 3-hydroxy-3-methylglutaryl-coenzyme A lyase deficiency. 7th International Congress of Inborn Errors of Metabolism, Vienna 1997, abstr. P 113
- Johns, D. R., A. G. Stein, R. Wityk:* MELAS syndrome masquerading as herpes simplex encephalitis. *Neurology* 43 (1993) 2471–2473
- Kohlschütter, A.:* Neuroradiological and neurophysiological indices for neurometabolic disorders. *Eur. J. Pediatr.* 153 (Suppl 1) (1994) 90–93
- Kotlarek, F., A. Thron, U. Weber, R. Schneider:* Der Schlaganfall beim Kind: Ätiologie, Differentialdiagnose, sinnvolle Diagnostik und therapeutische Möglichkeiten. *Klin. Pädiatr.* 205 (1993) 332–339
- Leibel, R. L., V. E. Shih, S. I. Goodman et al:* Glutaric acidemia: a metabolic disorder causing progressive choreoathetosis. *Neurology* 30 (1980) 1163–1168
- Leonard, J. V., M. E. Pembrey, C. A. Oley, B. N. Harding:* Neuropathologic changes in ornithine carbamoyl transferase deficiency. *J. Pediatr.* 109 (1986) 1074
- Lowry, O. H., N. J. Rosebrough, A. L. Farr, R. J. Randall:* Protein measurement with the Folin phenol reagent. *J. Biol. Chem.* 193 (1951) 265–275
- Maertens, P., R. Richardson, F. Bastian, J. P. Williams, F. Hommes:* A new type of mitochondrial encephalomyopathy with stroke-like episodes due to cytochrome oxidase deficiency. *J. Inher. Metab. Dis.* 11 (Suppl 2) (1988) 186–188
- Mamourian, A. C., A. du Plessis:* Urea cycle defect: a case with MR and CT findings resembling infarct. *Pediatr. Radiol.* 21 (1991) 594–595
- McLean, P., E. Reid, M. W. Gurney:* Effect of azo-dye carcinogenesis on enzymes concerned with urea synthesis in rat liver. *Biochem. J.* 91 (1964) 464–473
- Natowicz, M., R. I. Kelley:* Mendelian etiologies of stroke. *Ann. Neurol.* 22 (1987) 175–192
- Pavlakis, S. G., P. C. Phillips, S. Di Mauro, D. C. de Vivo, L. P. Rowland:* Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke like episodes: a distinctive clinical syndrome. *Ann. Neurol.* 16 (1984) 481–488
- Riikonen, R., P. Santavuori:* Hereditary and acquired risk factors for childhood stroke. *Neuropediatrics* 25 (1994) 227–233
- Schoenberger, B. S., J. F. Mellinger, D. G. Schoenberger:* Cerebrovascular disease in infants and children. A study of incidence, clinical features and survival. *Neurology* 28 (1978) 763–768
- Shih, V. E., I. F. Abrams, J. L. Johnson et al:* Sulfite oxidase deficiency. *N. Engl. J. Med.* 297 (1977) 1022–1028
- Steen, C., R. Baumgartner, M. Pegel, T. Suormala, W. Lehnert, M. Duran et al:* Acute late-infantile manifestation with metabolic stroke in isolated 3-methylcrotonyl-CoA carboxylase deficiency (MCCD). 33rd Annual Symposium Toledo, SSIEM abstr. P070 (1995) 74
- Tanaka, K. R., D. E. Paglia:* Pyruvate kinase and other enzymopathies of the erythrocyte. In: *The Metabolic and Molecular Bases of Inherited Disease.* (C. R. Scriver, A. L. Beaudet, W. S. Sly, D. Valle, eds.) 7th Edition, McGraw-Hill Inc, 3485–3511

- ⁴⁰ Thompson, G. N., J. Christodoulou, D. M. Danks: Metabolic stroke in methylmalonic acidemia. *J. Pediatr.* 115 (1989) 499–500
- ⁴¹ Vallée, L., M. Fontaine, J. P. Nuyts, G. Ricart, I. Krisovic, P. Divry et al: Stroke, hemiparesis and deficient mitochondrial β -oxidation. *Eur. J. Pediatr.* 153 (1994) 598–603
- ⁴² Van Lierde, A., D. Colombo, L. N. Rossi, F. Marchesi, M. Giani, G. Consalvo et al: Hemiparesis in a girl with cystinosis and renal transplant. *Eur. J. Pediatr.* 153 (1994) 702–703

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