biogenesis disorders. We present a family with 3 affected children in whom plasma VLCFA profiles normalized with aging.
Cases: The index patient, a boy, youngest of 11 children, presented at day 5 with convulsions. MRI of the brain showed polymicrogyria. In plasma an elevated C26:0 level (2.88 μmol/l) and elevated ratios of C24/C22 and C26/C22 were found, which was also seen in fibroblasts. Furthermore, fibroblasts showed a diminished DHAPAT activity and an abnormal catalase immunofluorescence profile indicative of absence of peroxisomes. Molecular analysis of the PEX6 gene showed two pathogenic mutations c.2362G>A (p.Val788Met) and c.2734G>A (p.Ala912Thr). These mutations were also found in two older siblings with intellectual disability. Both have no speech, normal hearing and vision, and are wheelchair bound. Their plasma VLCFA profiles were normal, only pristanic acid and pipecolic acid were elevated.
Conclusion: Peroxisomal defects can be missed by standard laboratory investigations in plasma.

P-498

Nonsense mediated mRNA decay affects nonsense transcripts levels and in vitro response to gentamicin and ataluren in X-ALD

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Background: X-linked adrenoleukodystrophy (X-ALD) is caused by mutations in the ABCD1 gene, characterized by increased concentrations of very long-chain fatty acids due to a defect in peroxisomal β-oxidation. Aminoglycosides and PTC124 can readthrough premature termination codons (PTCs) allowing the translation of full length proteins. Response to drugs was found only in patients with the higher level of mRNA. Nonsense-mediated mRNA decay (NMD) is a mechanism which degrades transcripts carrying PTCs and has an important role in response to treatments to promote readthrough. UPF1 RNA helicase is involved in this pathway.
Objectives: To prove aminoglycosides and PTC124 in fibroblast cultures from patients with X-ALD. To analyzed NMD efficiency in X-ALD fibroblasts.
Materials and Methods: Fibroblasts from patients (p.Trp137*, p.Ser290*, p.Arg464*) were treated with different doses of gentamicin and PTC124. Protein expression was analyzed by Western blot. NMD was directly inhibited by using siRNA against UPF1 and indirectly by Cicloheximide. Levels of mRNA were determined by qPCR.
Results: We didn't detect any increase in PALD expression after treatment with PTC124 or gentamicin. Downregulation of NMD increases the level of ABCD1 transcripts in two patients.
Conclusions: Aminoglycoside therapy doesn't improve X-ALD for the mutations analyzed. NMD affects the level of many ABCD1 transcripts.

P-499

Disturbed brain cholesterol homeostasis in inborn-errors of metabolism: a common denominator?

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Background: Cholesterol is a key molecule needed for proper brain development and functioning and is locally synthesized since it cannot be imported from the blood. Brain cholesterol homeostasis comprises the brain-specific CYP46A1 enzyme, which can hydroxylate cholesterol in its more polar 24-hydroxycholesterol (24OHC), a blood-brain barrier permeable molecule.
Objectives: Brain cholesterol synthesis depends on the mitochondrial formation of citrate serving as cytosolic acetyl-CoA donor. We investigate whether impaired brain cholesterol synthesis is a common denominator in inborn errors of metabolism by investigating the plasmatic levels 24OHC.
Methods: 24OHC is measured in plasma samples by SID-GC-MS. The analytical procedure comprises a solid-phase extraction step to selectively isolate multiple-hydroxylated cholesterol derivatives.
Conclusion: We have defined 24OHC reference values: a unique age dependent profile was found whereby 24OHC is low (50nM) in the neonatal period followed by a steep incline with its maximum at 1,5 yrs (450nM), followed by a slow decline to 50nM at 12 yrs, after which the levels of 24OHC are stable. Plasma samples from individuals affected with PDH deficiency, combined D/L-2HGA, SLOS, Niemann Pick C and PKU have been assessed. For the majority of these samples, the levels of 24OHC deviate from the average of the reference values.

P-500

Spinal cord anomalies in Smith-Lemli-Opitz syndrome (SLOS) new addition to the phenotype spectrum

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Background: Smith Lemli Opitz Syndrome (SLOS), the most common inborn error of sterol metabolism, includes a host of neurodevelopmental and behavioral findings. Cholesterol is necessary for sonic hedgehog signaling, thus, a potent morphogen influencing embryonic neurodevelopment. Known SLOS neurodevelopmental / CNS phenotype includes a variety of structural abnormalities of the cerebrum and cerebellum.
Purpose: Our study expands the neurodevelopmental phenotype spectrum to report on spinal cord and spinal column malformations in SLOS.
Methods: As part of the SLOS natural history protocol in progress at the NIH, medical records were reviewed for clinical symptoms potentially related to the spinal cord.
Results: 6 patients with radiological evidence of spinal cord or spinal column abnormality were identified. The spine and spinal cord findings included: scoliosis, spina bifida occulta, spinal cord syrinx, type 1 Chiari malformation, caudal agenesis, and Klippel-Feil anomaly. Even after identification of these abnormalities, some patients had unexplained clinical neurological symptoms.
Conclusion: We suspect the same neurodevelopmental pathogenesis involving sonic hedgehog signaling implicated with cerebrum and cerebellum malformation in SLOS, may also cause spinal cord and spinal column malformations in SLOS. Investigations of unexplained neurological symptoms with MRI and ultrasound of the spine can lead to identification of surgically correctable abnormalities.

P-501

Mass spectrometric analysis of urinary steroids allows for the diagnoses of essential hypertension, resistant to classical treatment

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Hypertension is a ubiquitous health problem. A significant proportion of hypertensive patients are resistant to conventional therapy, and identification