

acidemia, 1 3-OH-metilglutaric aciduria, 1 glutaric aciduria type 1, 1 metilglutaconic acidemia, 1 trimethylaminuria, 1 propionic acidemia, 2 tyrosinemia and 3 homocystinuria. Ventilatory support needed in 13/20, vasoactive agents 11/20, peritoneal dialysis 8/20, continuous veno-venous haemofiltration 4/20. 8 patients died; among survivors, 2/12 maturative failure, 3/12 serious neurological sequelae, 1/12 liver failure, needing transplantation.

**Conclusions** Aminoacidopathies diagnosed by Ms/Ms start early with treatment. Wide range of presentation symptoms and findings.

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#### THE NIEMANN-PICK TYPE C SUSPICION INDEX TOOL: EXAMINATION OF ITS DISCRIMINATORY POWER BY AGE AND ASSOCIATIONS BY LEADING SYMPTOMS

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**Background and Aims** The Suspicion Index (SI) screening tool was developed to identify suspected patients with Niemann-Pick disease type C (NP-C, Neurology, 2012). The SI provides Risk Prediction Score (RPS) based on NP-C symptoms within and across domains (visceral, neurological, and psychiatric). To further examine a) discriminatory power of the SI by age and b) symptom-associations by NP-C suspicion-level and leading symptoms.

**Methods** The original retrospective data were split into three age groups, where NP-C positive cases were: >16 years (n=30), 4–16 years (n=18), and < 4 years (n=23), and patients' RPS was analysed by logistic regression. Co-occurrence of symptoms within groups of suspicion-level (low, medium, and high) and leading symptoms (presence/absence of ataxia, cognitive decline, psychosis, and splenomegaly) were analysed descriptively.

**Results** NP-C positive cases vs. controls showed strong discriminatory power of RPS. Area under the Receiver Operating Characteristic curve was 0.964 (>16 years) and 0.981 (4–16 years) but a weaker 0.562 for infants (< 4 years). Patients with RPS < 70 were characterised by a lack of psychiatric symptoms and low levels of neurological involvement, suggestive of a more visceral phenotype. In patients >4 years, prominent leading symptoms' associations were: ataxia with "dystonia, dysarthria/dysphagia and cognitive decline"; psychosis with "dysarthria/dysphagia"; and psychotic symptoms with "cognitive decline and treatment-resistant psychiatric symptoms".

**Conclusions** The SI tool maintains strong discriminatory power in patients >4 years but is not as useful for infants < 4 years. The SI is informative regarding the association and co-occurrence of symptoms in patients with NP-C.

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#### CENTRAL NEUROGENIC HYPERVENTILATION MAY CAUSE METABOLIC ALKALOSIS IN MITOCHONDRIAL ENCEPHALOPATHY

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**Background** The differential diagnosis of respiratory alkalosis (RA) includes a state called central neurogenic hyperventilation (CNH). In the few reported cases of CNH the etiology was a stimulation of the respiratory center by an infiltrative tumor in the cerebral pons. In some cases, a shift in the cerebral pH to acidic range was also hypothesized.

**Case Report** We report the case of a six year-old boy with a known Pearson syndrome, a mitochondrial disorder affecting bone marrow, pancreas and renal tubules. He was admitted to our PICU with deteriorating mental status and compensated metabolic acidosis (lactic, hyperchloremic and tubular). On admission, blood gas analysis showed a pH of 7.30 with a disproportionately low compensating pCO<sub>2</sub> of 10 mmHg (HCO<sub>3</sub> 4.9 mmol/L). Serum HCO<sub>3</sub> normalized by substitution (21.0 mmol/L), when he developed a RA (pH 7.51, pCO<sub>2</sub> 24 mmHg) persisting over 48 hours, even during sleeping periods. After reviewing his previous blood gas results, this phenomenon was present for years. After excluding known etiologies of RA, we suspected CNH caused by intra-cerebral acidosis. The pH and HCO<sub>3</sub> were lower, while lactate was higher in cerebro-spinal fluid than in serum. An MR spectroscopy confirmed cerebral lactate accumulation, showing a peak in the posterior cerebrum. Encephalopathy is not among the classic manifestations of Pearson syndrome.

**Conclusion** We were able to demonstrate elevated local lactate level leading to intra-cerebral acidosis, stimulation of the respiratory center and causing long-standing hyperventilation. This phenomenon adds a new aspect to the complex clinical picture of mitochondrial disorders.

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#### A HYPOTONIC INFANT WITH METHYLENE TETRAHYDROFOLATE REDUCTASE (MTHFR) DEFICIENCY; HOMOZYGOUS MUTATION OF C.1015T>G IN MTHFR GENE

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**Background** Methylene tetrahydrofolate reductase (MTHFR) deficiency is a rare autosomal recessive disorder, caused by mutated alleles of the MTHFR gene. Since this enzyme catalyzes the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, its deficiency results in hyperhomocysteinemia, homocystinuria and hypomethionemia. The clinical manifestations vary from asymptomatic to fatal disease with severe neurodevelopmental delay and epileptic encephalopathy.

**Case** Our patient was a two-month old female born from consanguineous parents presenting with infantile spasms, hypotonia and microcephalus. She was transferred to our pediatric intensive care unit for respiratory failure. The biochemical work-up revealed low vitamin B12 level: 152.6 pg/ml (197–866 pg/ml), close to lower limit of folate: 4.62 ng/ml (3.1–17.5 ng/ml), increased homocysteine level: 9.85 nmol/ml (0–1 nmol/ml), and very low methionine level: 7.32 nmol/ml (19–51 nmol/ml). Magnetic resonance imaging of the brain showed white matter changes of the frontal lobes, posterior legs of capsula interna, pons and nucleus dentatus consistent with demyelination. MTHFR deficiency was suspected, and treatment with folic acid, vitamin B12, methionine and betaine was initiated. The peripheral blood DNA analysis of the patient demonstrated a homozygous mutation of c.1015T>G in MTHFR gene. Both parents were confirmed to be asymptomatic heterozygote carriers. Despite treatment, the prognosis was fatal.

**Conclusions** As related reports suggest better prognosis with early treatment, pediatricians need to consider MTHFR deficiency in similar cases. Prenatal diagnosis is available and should be encouraged for the future pregnancies.

### 1035 THE INTERNATIONAL REGISTRY FOR NIEMANN-PICK DISEASE TYPE C (NP-C) IN CLINICAL PRACTICE

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**Background and Aim** An international disease registry was started in September 2009 to evaluate the long-term disease course of NP-C in clinical settings.

**Methods** Descriptive data from enrolment are presented for all patients with available data who were included in the Registry as of 19<sup>th</sup> August 2011.

**Results** 121 patients have been enrolled. The median (range) age at enrolment was 16.9 (0.9–56.6) years, age at onset of neurological manifestations was 8.2 (< 1–48.0) years (n=100), and age at diagnosis was 11.8 (0.1–53.9) years (n=110). A history of neonatal jaundice was recorded in 4/4 evaluable patients with early-infantile (EI) onset of neurological manifestations (at age < 2 years; n=9), 6/21 (29%) with late-infantile (LI) onset (at 2 to < 6 years; n=31), 6/21 (29%) with juvenile (JUV) onset (at 6 to < 15 years; n=31), and 3/20 (15%) with adolescent/adult (AA) onset (at ≥ 15 years; n=29). Miglustat therapy at enrolment was recorded in 88/121 (73%) patients; mean (SD) exposure 1.69 (1.85) years (n=86). Neurological manifestations were observed in 71/84 (85%) patients: ataxia (71%), vertical gaze palsy (68%) and dysarthria (62%) were most frequent. Median (range) disability scores (0=normal; 1=worst) were: 0.0 (0.0–0.94) in EI (n=7), 0.29 (0.0–1.0) in LI (n=28), 0.41 (0.15–0.88) in JUV (n=28), and 0.29 (0.06–0.81) in AA-onset patients (n=26). A low proportion of patients had normal language, manipulation, ambulation, and/or swallowing.

**Conclusions** Over two-thirds of this NP-C cohort had infantile or juvenile onset of neurological manifestations; neonatal jaundice was observed more frequently in these patients *versus* adolescent/adult-onset patients.

### 1036 GRACILE SYNDROME IN A TURKISH NEWBORN INFANT CAUSED BY A HOMOZYGOUS MUTATION (P99L) IN COMPLEX III ASSEMBLY FACTOR BCS1L

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**Background and Aim** GRACILE syndrome, a neonatal, autosomally recessive disorder found in Finland, featuring growth retardation, aminoaciduria, cholestasis, iron overload, lactic acidosis and early death, is caused by a homozygous mutation (S78G) in BCS1L, the assembly factor for respiratory chain complex III. We investigated a newborn Turkish girl with similar symptoms. Her two sisters with low birth weight, metabolic acidosis, cholestasis and renal Fanconi syndrome, had died at 18 and 105 days age, respectively.

**Methods and results** The girl was born to healthy nonconsanguineous parents. She was growth retarded (1789 g at term), developed tachypnea and metabolic acidosis on day one. Lactic acidosis, jaundice with direct hyperbilirubinemia, nonspecific aminoaciduria, high phosphaturia, proteinuria and glucosuria were detected. Serum

iron (190 mcg/dl), ferritin (2819 ng/ml) and transferrin saturation (99.4%) were increased. Metabolic, cardiologic and sonographic workup were otherwise normal. Because of similarities with GRACILE syndrome, the *BCS1L* gene was investigated. The Finnish SNP was not found, but gene sequencing revealed a homozygous mutation resulting in an amino acid exchange (P99L) in the protein.

**Conclusions** The studied infant had a GRACILE-like disorder caused by a different mutation than that in newborns of Finnish ancestors. Most likely the two diseased siblings had the same homozygous BCS1L mutation that previously has been published in three other newborns or Turkish origin. We proposed that P99L-mutation in BCS1L is a Turkish genotype resulting in GRACILE syndrome phenotype, and should be investigated in Turkish newborns with the typical clinical features.

### 1037 DETERMINATION OF PREALBUMIN, SELENIUM, ZINC AND IRON CONCENTRATION IN SERUM FOR MONITORING THE NUTRITION STATUS OF PHENYLKETONURIC AND HYPERPHENYLALANINEMIC PATIENTS

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**Background and Aims** Phenylketonuria is an inherited disorder of metabolism of the amino acid phenylalanine caused by a deficit of the enzyme phenylalaninhydroxylase. It is treated with a low-protein diet containing a low content of phenylalanine to prevent mental affection of the patient. The objective of the present study was to assess the compliance of our phenylketonuric (PKU) and hyperphenylalaninemic (HPA) patients; to determine the concentration of serum pre-albumin and trace elements to discover the potential correlation between the amount of proteins in food and their metabolic control.

**Methods** The prospective study contained altogether 174 patients, of which 113 were children, 60 with PKU and 53 with HPA and 61 were adults, 51 with PKU and 10 with HPA.

**Results** We did not prove a statistically significant difference in the levels of serum pre-albumin, zinc and iron among the respective groups. We proved statistically significant difference in the level of serum selenium among PKU and HPA patients in adulthood (p=0.006, Mann-Whitney U test).

**Conclusion** The therapeutic restrictive diet for PKU and HPA makes the patient liable to the risk of nutritional deficit.

### 1038 UREA CYCLE DEFECTS- MISDIAGNOSES AND WRONG DIAGNOSES

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**Background** Urea cycle defects (UCD) constitute a group of rare metabolic disorders that involve the enzymes of every step of urea cycle. Deficiency of one of these enzymes leads to hyperammonemia and they present classically with acute life-threatening neonatal encephalopathy. However, presentation at later childhood or adulthood could also occur. There are many disorders that mimic UCD causing misdiagnosis or wrong diagnosis.

**Methods** A prospective and retrospective study was made on 10 cases of UCD. Most have been diagnosed at the neonatal period with follow up done through our genetic and metabolic clinic at Naser Pediatric Hospital.

**Results** Most of the cases presented with acute ammonia encephalopathy. Age of presentation was variable. Most of the cases were from the Northern Gaza which is of geographical similarity to distribution of the IEM collectively. There was no gender differences.