P3.17
The extremes of the clinical spectrum of CMT1A and HNPP patients: Phenotypic characteristics
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Charcot-Marie-Tooth disease type 1A (CMT1A) and hereditary neuropathy with liability to pressure palsies (HNPP) are autosomal dominant peripheral neuropathies caused by copynumber variation of the PMP22 gene. The clinical variability of these disorders is wide, between as well as within families. This variability suggests the presence of modifiers. We previously identified cases of double trouble (the presence of two mutations in CMT-related genes) in severely affected patients, i.e. known CMT genes can act as modifiers. We are conducting a search for genetic modifiers of PMP22 related neuropathies by selecting the extremes of the phenotypic spectrum of CMT1A and HNPP patients, based on disability measured by the Overall Neuropathy Limitation Scale (ONLS). The ONLS was taken by telephone interview in 224 CMT and 114 HNPP patients. The ONLS has a minimum score of 0, meaning no disability and a maximum score of 12, meaning not being able to make purposeful movements with arms and legs. The ONLS shows a Gaussian distribution for both disorders. The median score for CMT patients is 4 and for HNPP patients 3. Mildly affected patients (ONLS <2) and CMT patients with a score >5 and HNPP patients >4 representing the extreme phenotypes are clinically evaluated to further characterize disease severity. Clinical evaluation involves neurological examination, including extensive sensory testing and dynamometry of foot dorsiflexion and three point grip and Charcot-Marie-Tooth Neuropathy Score (CMTNS). Hand function testing and 10- and 50-meter timed walking tests are done. The 30 genes known to be involved in CMT will be analysed in these patients.

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P3.18
Hereditary polyneuropathies in a neuromuscular pediatric consultation
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Published pediatric polyneuropathies series differ from adult series in many ways. There is a lower incidence of toxic neuropathies and due to systemic diseases, as well as chronic idiopathic polineuropathy. The incidence of inherited neuropathies, including metabolic disease and central nervous system pathology, is much higher. To characterize the profile of hereditary polyneuropathies followed in a neuromuscular consultation in a Portuguese Tertiary Pediatric Hospital. All patients with confirmed hereditary neuropathy were selected from the neuromuscular consultation database. We selected patients observed between 2000 and 2011, and reviewed their clinical files. We found 25 patients, 17 (68%) presenting an isolated polyneuropathy, and in the remaining the polyneuropathy was part of a more complex disease. The neuropathological studies revealed demyelinating neuropathy more frequently in the isolated polyneuropathy group. Age of clinical onset was later in this same group, being the main initial complaints gait difficulties. Definite diagnosis was achieved in 47% of these patients among which stands out the mutation on CMT1A gene (72%). In the other group diagnosis was established only in 25% of patients. Hypotonia was the onset manifestation and all patients from this group developed moderate to severe cognitive impair-
ment. From the total of patients only 10 (40%) had positive family history. Nerve biopsies had been performed in 9 (35%), being useful to the diagnosis in two of them. According to the last clinical registration, 8 patients are currently in wheelchair (32%). A definitive diagnosis was not always possible, even after extensive investigation. Our data probably underestimates patients with more complex diseases, once electromyography is not routinely performed. Although there is no specific therapy, the diagnosis has important implications for these patients’ follow-up and genetic counseling.

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P3.19
Neonatal presentation of Charcot-Marie-Tooth disease: A new mutation in Mitofusin 2 gene
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Charcot-Marie-Tooth (CMT) is a heterogeneous group of inherited peripheral neuropathies with a prevalence of 1/2500. The Mitofusin 2 has an essential role in axonal transport of mitochondria, as well as in controlled fusion of its membrane, so there are frequent changes of some mitochondrial respiratory chain complexes (I, II, III, V). Young boy 3 years old without a family history of neuromuscular disease. In the neonatal period he had a marked hypotonia and swallowing difficulties. At 7 months he was referred for consultation for motor delay. Clinical examination revealed flaccid tetraparesis predominantly distal in lower limbs with axial involvement. No heart disease and no respiratory compromise and a preserved bulbar function. The electromyographic study showed a severe axonal neuropathy. The brain MRI revealed white matter alterations in both semi-oval centers. The electroencephalogram (EEG) was immature, poorly structured with paroxysmal activity during sleep. Molecular analysis of the gene MFN2 revealed a de novo pathogenic missense mutation in the vicinity of the GTPase domain, very close to a well known mutational hotspot, c.272T>A (p.Val91Glu) in exon 4, in heterozygosity, not found in the parents. The authors present an atypical form of CMT2A2 with a mutation in the gene MFN2 not previously described, which broadens the clinical and molecular spectrum of the rare HMSN2A.

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P3.20
Inherited peripheral neuropathies: Genetic testing in the diagnostic laboratory
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Charcot-Marie-Tooth is a group of clinically and genetically heterogeneous disorders with over 40 genes implicated. The Genetics laboratory in Bristol, UK, currently offers screening for 12 genes involved in CMT1, CMT2, dHMN and HSAN phenotypes. The referrals over the last three years were reviewed. A total of 775 patients were tested using MLPA (MRC-Holland) for PMP22 dosage abnormalities. 125 CMT1 referrals were 17p11.2 duplication positive (125/443, 28%), and 90 HNPP referrals were 17p11.2 deletion positive (90/332, 27%). A total of 488 patients were further screened for point mutations in one or more of the PMP22, GJB1, MPZ, MFN2, NEFL, EGR2, and PRX genes, using high throughput semi-automated direct sequencing analysis. Results were analysed using Mutation Surveyor software (SoftGenetics). Eighty one sequence variants were detected; 57 previously described mutations and 44 novel variants. Pathogenic mutations were finally confirmed in 60 patients. PMP22 point mutations accounted for 5.3% of CMT1 and 11.5% of HNPP patients;
A novel pathogenic mutation of the MPZ gene causing hereditary neuropathy

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Charcot Marie Tooth disease type 1 is the most common inherited neuropathy. It is a genetically heterogeneous group of disorders. Mutations in the myelin protein zero (MPZ) gene have earlier been associated with CMT type IB, with Dejerine Sottas Disease (DSD) or with Congenital Hypomyelinating neuropathy (CH). Over 115 distinct mutations in the MPZ gene have been reported for CMT 1B patients. A three year old girl presented at the age of 2 years and 9 months with delayed motor milestones. Her father previously had delayed motor milestones and now showed pes cavus and clinical and electrophysiological signs of a demyelinating polyneuropathy. Neurological exam of our patient showed an unsteady stepping gait, hypertension of the knees, hypermobile joints, absent tendon reflexes and the patient needed some help of her arms to get up from a sitting position. Our patient and her father had an identical heterozygous mutation c.118A>T in the MPZ gene (form the HVGS nomenclature, or c.88A>T, p.Ile30Phe as in other literature). As our patient and her father share a comparable phenotype, it is assumed that this mutation is pathogenic. Although several mutations in codon 40 of the MPZ gene have been described earlier, this specific pathogenic mutation has not been described before.

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