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Abstract: Mitochondrial diseases are a heterogeneous group of diseases with different phenotypes and genotypes. Headache and, particularly migraine, seems to occur often in patients with MELAS and in patients with CPEO phenotypes. The International Classification of Headache Disorders (ICHD-3 beta) has classified headache as a secondary entity only in MELAS patients. Other headache phenotypes in mitochondrial diseases are not considered in ICHD-3beta. In this study, we analyzed headache phenomenology in a large group of patients with mitochondrial disorders. A cross-sectional questionnaire-based study on 85 patients with mitochondrial disease with different genotypes and phenotypes was conducted between 2010 and 2011. A structured headache questionnaire according to ICHD-2 was used followed by a telephone interview by a headache expert. Prevalence and characteristics of headache could be analyzed in 42 patients. Headache diagnosis was correlated with genotypes and phenotypes. In addition, the mtDNA haplotype H was analyzed. Headache was reported in 29/42 (70%; 95% CI, from 55.1 to 83.0%) of the patients. Tension-type headache (TTH) showed the highest prevalence in 16/42 (38%; 95% CI, from 23.4 to 52.8%) patients, followed by migraine and probable migraine in 12/42 (29%; 95% CI, from 14.9 to 42.2%) patients. Nine of the 42 (21%; 95% CI, from 9 to 33.8%) patients
reported two different headache types. Patients with the mtDNA mutation m.3243A> G (n = 8) and MELAS (n = 7) showed the highest prevalence of headaches (88% and 85%, respectively). In patients with the CPEO phenotype (n = 32), headache occurred in 14/18 (78%; 95% CI, from 58.6 to 97%) of patients with single deletions, and in 7/13 (54%; 95% CI, from 26.7 to 80.9%) patients with multiple mtDNA deletions. There were no association between the mtDNA haplotype Hand the headache-diagnosis. The prevalence of headache was higher in patients with mitochondrial diseases than reported in the general population. In all phenotype and genotype groups, TTH was more frequent than migraine. The data also show that the current ICHD-3 beta exclusively focused on MELAS syndrome as vasculopathy does not consider the broader spectrum of headache phenotypes in mitochondrial disorders.