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Hippocampal sclerosis and mesial temporal lobe epilepsy in chorea-acanthocytosis: A case with clinical, pathologic, and genetic evaluation

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Chorea-acanthocytosis (ChAc) is an autosomal recessive neurodegenerative disease associated with mutations in *VPS13A* that encodes the protein chorein. ChAc is characterized by progressive chorea, dystonia, and psychiatric symptoms, developing in young adulthood, often with acanthocytosis in peripheral blood. Tongue protrusion, or feeding dystonia, is common, as are seizures and neuropathy [1]. On neuropathology, there is basal ganglia atrophy, neuronal loss, and gliosis, especially in the caudate nucleus [2]. We report the case of a patient with ChAc with hippocampal sclerosis who had extensive longitudinal follow-up, including neuropathology and general autopsy.

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The patient was a 51-year-old Caucasian male with clumsiness, tics, and dysarthria since adolescence. At age 32, he developed anxiety, inattention, confusional episodes, memory problems, personality changes, and seizures with aura, staring, decreased awareness, head turning, and secondary generalization. Seizures were difficult to control in spite of multiple medications. There was no family history of neurologic, psychiatric, or cardiac disorders, except for dementia in his maternal grandmother. He never used tobacco, alcohol, or drugs. On presentation at age 33, his examination was significant for chorea, dysarthria, facial and vocal tics, and slightly decreased vibration sensation as well as hyporeflexia. He had uncontrolled tongue protrusion while eating. Neuropsychological evaluation revealed impaired verbal memory and decreased processing speed on Hopkins List Learning, Wechsler Memory Scale Third Edition, and Wechsler Adult Intelligence Scale Third Edition Processing Speed tests. Fresh EDTA-anticoagulated saline-diluted peripheral blood smear showed 50% acanthocytes. Creatine kinase (CK) was elevated to between 1541 and 4490 U/L (normal 52–386 U/L), as were transaminases with ALT 66–98 U/L and AST 67–96 U/L. Serial brain MRIs revealed bilateral caudate nucleus atrophy and mesial temporal hyperintensities (Figures 1A–C). Electroencephalography (EEG) demonstrated interictal bitemporal spikes; electromyography/nerve conduction testing confirmed chronic generalized sensorimotor axonal polyneuropathy. Genetic testing showed compound heterozygous mutations in *VPS13A* (proband 21 in [3]).

Progressive worsening of chorea resulted in frequent falls. By age 48, he was wheelchair-dependent with mild diffuse weakness (4/5 strength on the Medical Research Council scale). During hospitalization for percutaneous endoscopic gastrostomy for severe dysphagia, he developed bradycardia (30 beats per minute) diagnosed as sick sinus syndrome that required pacemaker implantation. Echocardiogram showed mild global hypokinesis with a left ventricular ejection fraction of 45–50%. The patient expired at age 51 in a nursing home from sepsis.

A full autopsy was performed 8 hours after death, with written consent, including consent for research, from the patient's next of kin. The patient and his legal representative had also provided informed consent for participation in research studies approved by the National Institutes of Health Institutional Review Board. External examination was significant for diffuse muscle atrophy. Aspiration pneumonia was identified as cause of death. The brain weighed 1550 g. The left cerebral hemisphere was frozen. The right hemisphere was fixed in 10% neutral buffered formalin. Superior frontal gyrus, cingulate gyrus, primary motor cortex, primary somatosensory cortex, primary visual cortex, temporal pole, hippocampus, pre- and post-commissural basal ganglia, amygdala, thalamus, midbrain, pons, medulla, cerebellum and spinal cord sections were obtained. Stains included hematoxylin and eosin, Bielschowsky silver stain, and beta-amyloid, phospho-tau, and glial fibrillary acidic protein immunohistochemistry. Masson trichrome staining was performed on myocardium and liver (see Supplementary Material for further details).

Gross neuropathology showed striking caudate nucleus atrophy bilaterally (Figures 1D & 1E). Putamen and globus pallidus were also atrophic. There was severe neuronal loss and gliosis in caudate, putamen, and globus pallidus (Figures 1H–J). The right hippocampus was more atrophic than the left (Figures 1F & 1G) with neuronal loss and gliosis in CA1, CA3,

and CA4 subfields, and possible granule cell dispersion in the dentate gyrus (Figures 1K–M), consistent with International League Against Epilepsy Type 1 hippocampal sclerosis (HS) [4]. Of note, the CA2 subfield and subiculum were spared. The rest of the cerebral hemispheres, including temporal neocortex, amygdala, thalamus, and mammillary bodies, and brainstem were unremarkable.

There were significant pathologic changes in the heart and liver. Notably, the heart weighed 430 grams. Coronary arteries were patent with 10% atherosclerosis. Microscopically, left and right ventricle myocardium showed diffuse myocyte hypertrophy, myocyte nuclear size variation, patchy mild myofiber disarray, and patchy interstitial fibrosis (Figures 1N & 1O). These nonspecific changes and increased heart weight are indicative of idiopathic dilated cardiomyopathy (DCM) [5]. In the liver, abnormalities were only seen microscopically. There was a small amount of perivenular fibrosis and sinusoidal dilation and congestion (Figure 1P), consistent with congestive hepatopathy.

To exclude other genetic correlates, whole exome sequencing (WES) was performed on DNA previously extracted from whole blood. Briefly, WES was performed using a high-throughput sequencing system (HiSeq 2500, Illumina, San Diego, CA, USA) with average coverage of 66X. Subsequent bioinformatics analysis included alignment of DNA sequence reads, removal of sequencing artifacts, and annotation, filtering and functional prediction of variants (refer to Supplementary Methods for further details). Genes associated with neuroacanthocytosis syndromes were searched [1]. In *VPS13A*, 3283G>C and 4835delC were found, which were previously identified by restriction enzyme analysis [3]. No variants were found in *XK*, *JPH3*, and *PANK2*. Genes implicated in DCM [6], in mesial temporal lobe epilepsy with hippocampal sclerosis [7], and other epilepsies [8] were also searched but no relevant mutations were found.

In summary, this is a case of ChAc with extensive clinical, neuropathological, and genetic characterization. In addition to basal ganglia atrophy with neuronal loss and gliosis, there were the uncommon findings of HS and DCM.

This patient had clinical and EEG evidence of mesial temporal lobe epilepsy for which HS is the most frequently seen neuropathologic correlate [4]. We assume that his mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS) is related to ChAc. Mesial temporal lobe epilepsy has been previously reported in ChAc [9]. In light of these observations, we suggest expanding the clinical and neuropathological phenotype of ChAc to include possible MTLE-HS in addition to basal ganglia pathology. Interestingly, this correlates with a ChAc mouse model in which there is hippocampal pathology with increased numbers of astrocytes [10]. Furthermore, *VPS13A* is expressed in the hippocampus (Genotype-Tissue Expression (GTEx) Portal, <http://www.gtexportal.org>; Human Protein Atlas, <http://www.proteinatlas.org>).

DCM is unusual in ChAc, with only one previously reported case [11]. The histopathology in this patient resembles the cardiomyopathy of the McLeod neuroacanthocytosis syndrome due to *XK* mutations [12]. We are confident in attributing DCM in this patient to ChAc

given the absence of significant atherosclerosis, mutations in DCM genes or *XX*, and history of toxic exposures and myocarditis.

Therefore, this case broadens the phenotypic spectrum of mutations in *VPS13A* with chorea-acanthocytosis, hippocampal sclerosis, and dilated cardiomyopathy. These findings may be helpful in guiding the evaluation and treatment of patients with chorea-acanthocytosis and intractable seizures in whom epilepsy surgery may be explored as an option for seizure control.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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KM drafted the manuscript, collected and analyzed data, and contributed to the study design. SK, MMH, and JFC collected and analyzed data. CG collected and analyzed data, and reviewed and critiqued the manuscript. AD collected data, and reviewed and critiqued the manuscript. BIK conceptualized the study, contributed to the study design, collected data, and reviewed and critiqued the manuscript. RHW conceptualized the study, and reviewed and critiqued the manuscript.

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Figure 1.

Brain MRI (A–C), gross brain images (D–G), and basal ganglia, hippocampus, heart and liver histopathology (H–P). A. T1-weighted brain MRI showing mild bilateral caudate nucleus atrophy (circled) at age 36 years; R, right hemisphere; L, left hemisphere. B. Progression of caudate atrophy (circled) at age 43 years on T1-weighted brain MRI. C. Bilateral hippocampal hyperintensities (circled) on fluid attenuated inversion recovery (FLAIR) MRI at age 43 years. D. Left caudate head and putamen atrophy (arrow), fresh brain. E. Right caudate head atrophy (arrow), fixed brain. F. Left hippocampus atrophy (arrow), fresh brain. G. Mild right hippocampus atrophy (arrow), fixed brain. H,I. Caudate neuronal loss and gliosis; J. Globus pallidus neuronal loss and gliosis; K. An area of the hippocampal dentate gyrus suspicious for granule cell dispersion; L. Neuronal loss and gliosis in the CA4 hippocampus subfield; M. Gliosis in the CA4 hippocampal subfield demonstrated with anti-glial fibrillary acidic protein (GFAP) immunostaining at 100x with inset at 400x; N. Myocyte hypertrophy and nuclear size variation, and myofiber disarray in the left ventricle free wall myocardium; O. Area of interstitial fibrosis in the left ventricular free wall myocardium; P. Perivenular fibrosis in the liver. H–L and N: H&E, M: anti-GFAP, O & P: Masson trichrome. Scale bars: 100 μ m in H–L and N–P, and 50 μ m in M.