Parkinsonism in a pair of monozygotic CADASIL twins sharing the R1006C mutation: a transcranial sonography study.

Michele Ragno1, Sandro Sanguinigi1, Antonio Manca2, Luigi Pianese3, Cristina Paci1, Alfons Berbellini4, Valeria Cozzolino3, Roberto Gobbatol1, Silvio Peluso5 and Giuseppe De Michele5.

1 Division of Neurology, Modena University Hospital, Modena, Italy
2 Department of Radiology, Italy, National Research Center of Aging INRCA, Ancona, Italy
3 Molecular Medicine Laboratory, Marzio Hospital, ASVR MARCHE AV5, Ascoli Piceno, Italy
4 Nuclear Medicine Department, AOCL, Ascoli Piceno, Italy
5 Department of Neurosciences and Reproductive and Obstetrical Sciences, Federico II University, Naples, Italy

Background. Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL), the most common hereditary cerebral small vessel disease, is caused by mutations in the NOTCH3 gene on chromosome 19. Clinical manifestations of CADASIL include recurrent transient ischemic attacks, strokes, cognitive defects, epilepsy, migraine and psychiatric symptoms. Parkinsonian features have variably been reported in CADASIL patients, but only a few patients showed a clear parkinsonian syndrome.

Objectives of the study. We reported two patients, a pair of monozygotic twins, carrying the R1006C mutation of the NOTCH3 gene and affected by a parkinsonian syndrome. For the first time, we use transcranial sonography (TCS) to assess basal ganglia abnormalities. TCS is an emerging tool in the study of parkinsonism. TCS examination is able to identify iron accumulation in basal ganglia as hyperechogenic areas and brain iron deposition is recognised both as a constant marker and also as a pathogenetic mechanism of Parkinson's disease (PD) and atypical parkinsonism.

Material and methods. Twin A. He was asymptomatic until the age of 74 years when he was admitted to the hospital and on the basis of normal routine blood and cerebrospinal fluid analysis and of the clinical and neuroimaging features, a diagnosis of CADASIL coma was suspected and genetic analysis showed the R1006C mutation in the exon 19 of NOTCH3 gene. At the age of 75 years, generalized slowness of movement gradually appeared. Neurological examination showed generalized lead-pipe rigidity, mainly involving the lower limbs, bilateral bradykinesia, and reduction in step length and velocity. The Unified Parkinsonism Rating Scale (UPDRS) Part III score was 18/108. Neuroimaging assessment evidenced only mild impairment of visuospatial and visuconstructional functions. [123]I-FP-CIT brain SPECT (DaTSCAN) images displayed a reduction of tracer uptake in putamen bilaterally. LRRK2 gene mutation, responsible for PD, was screened and excluded.

Twin B. He suffered from hypertension since age 73 and was being treated with antihypertensive drugs. He has never smoked and had participated actively in sports (amateur cycling) since youth. He was asymptomatic for typical CADASIL symptoms, but described a general motor slowing from age 75. On neurological examination, the patient showed generalized lead-pipe rigidity, mainly involving the lower limbs, diffuse bradykinesia, slightly prominent on the left, flexed posture, and gait slowing with reduced arm swing on the left side. His UPDRS score was 29/108. Neuropsychological tests revealed a mild cognitive impairment with a MMSE score of 23/30. DaT-scan showed marked reduction of tracer uptake in the right putamen.

As for the other twin, genetic screening ruled out pathological mutations in LRRK2 gene and revealed the R1006C mutation in the NOTCH3 gene. Monozygosity with his brother was confirmed with 10 genetic markers (99.9%). In both the patients we performed TCS through the temporal acoustic window of both sides using a dedicated equipment ultrasound.

Results. In the first twin, TCS showed a bilateral hyperechogenic pattern of substantia nigra (SN). In the other twin, TCS evidenced a right hyperechogenic pattern of the SN. In both the patients, lenticular nucleus (LN) showed a bilateral hyperechogenic pattern and the width of the 3rd ventricle was slightly increased.

Discussion. In this study, we describe a pair of monozygotic twins sharing the R1006C NOTCH3 gene mutation and presenting with a late onset slowly progressive parkinsonism. In both the twins, TCS study found a diffuse hyperechogenicity of the subcortical structures; it detected an increased area of SN hyperechogenicity bilaterally in Twin A, and an increased echogenicity of the right SN in Twin B. Both the twins presented LN bilateral hyperechogenicity with a slightly increased width of the third ventricle. Asymmetrical increased echogenicity of SN, without LN hyperechogenicity, has been repeatedly reported as a characteristic TCS finding in PD. Vascular parkinsonism (VP) has been examined by very few studies and, state of the art, these features cannot be considered a distinctive feature of VP. The TCS pattern found in our CADASIL patients is not characteristic neither for a PD nor for a VP and could be explained by the specific pathological features of CADASIL. An increased and diffuse iron accumulation in putamen and CN is recognized as an important feature in CADASIL (Sadun et al., 2012). In the CADASIL, the arteriopathy of the LN is selectively and massively involved by processes of vascular smooth muscle cells degeneration, loss of smooth muscle cells and fibrotic thickening (Miao et al., 2006). Taken together, these evidences may explain, although partially, the LN involvement.

Conclusions. Our cases concurrently confirm that parkinsonian phenotype may represent one of the CADASIL manifestations. We have yet reported 5 CADASIL patients with parkinsonism (Ragno, 2013) carrying the R1006C NOTCH3 mutation, found also in the twins described. These evidences suggest that NOTCH3 mutations should be considered in patients with vascular parkinsonism, especially if areas of altered signal in external capsule and anterior horn of lateral ventricle, as temporal lobes are visible on T2-weighted or FLAIR MRI images. The TCS pattern found in our CADASIL patients is not characteristic neither for a PD nor for a VP. It would be important to reproduce our TCS findings in a larger number of CADASIL patients, as well as to test their possible significance in differentiating CADASIL or VP from PD and/or other types of atypical Parkinsonian syndromes.

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