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

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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 *NOTCH3* gene and affected by a parkinsonian syndrome. For the first time in CADASIL patients, we use transcranial sonography (TCS) to assess basal ganglia abnormalities. TCS is an emerging tool in the study of parkinsonisms. 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 speed. The Unified Parkinson Disease Rating Scale (UPDRS) Part III score was 18/108. Neuropsychological assessment evidenced only mild impairment of visuospatial and visuoconstructional functions. ^{123}IFP-CIT brain SPECT (DaTSCAN) images displayed a reduction of tracer uptake in putamen bilaterally. *LRRK2* gene mutations, responsible for PARK8, were 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. Monozygocity 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 nuclei (LN) showed a bilateral hyperechogenic pattern and the width of the 3° 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 and 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, SN hyperechogenicity is not 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 usual in CADASIL (Liem et al., 2012). In CADASIL, the arterioles of the LN are selectively and massively involved by processes of vascular smooth muscle cells degeneration, loss of autoregulation mechanism, and fibrotic thickening (Miao et al., 2006). Taken together, these evidences may explain, although partially, the LN involvement on TSC in our CADASIL twins. 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.
This is the second report of CADASIL twins to date. The first one described a pair of monozygotic CADASIL twins with a different neurological picture, suggesting that lifestyle-related factors (smoking and physical activity in particular) and unknown environmental conditions may act on the same genetic background to cause phenotypic differences (Mykkanen K, 2009). In support of this hypothesis, we report two CADASIL twins asymptomatic for main CADASIL symptoms and presenting a parkinsonian syndrome late in life associated with a common neuroimaging picture with a similar type and distribution of vascular lesions. Our patients shared hypertension as the only cardiovascular risk, had participated actively in sports (tennis and cycling) from young adulthood, and have never smoked. Therefore, in our report the same lifestyle-related factors result to be associated to identical clinical and neuroimaging features.
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 part of the 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.Further studies are necessary to investigate if parkinsonism is associated with some specific mutations of *NOTCH3* gene, as R1006C, suggesting a possible genotype–phenotype correlation.
Moreover,our cases suggest that lifestyle-related factors (smoking and physical activity in particular) and unknown environmental conditions may act on the same genetic background to cause phenotypic differences.

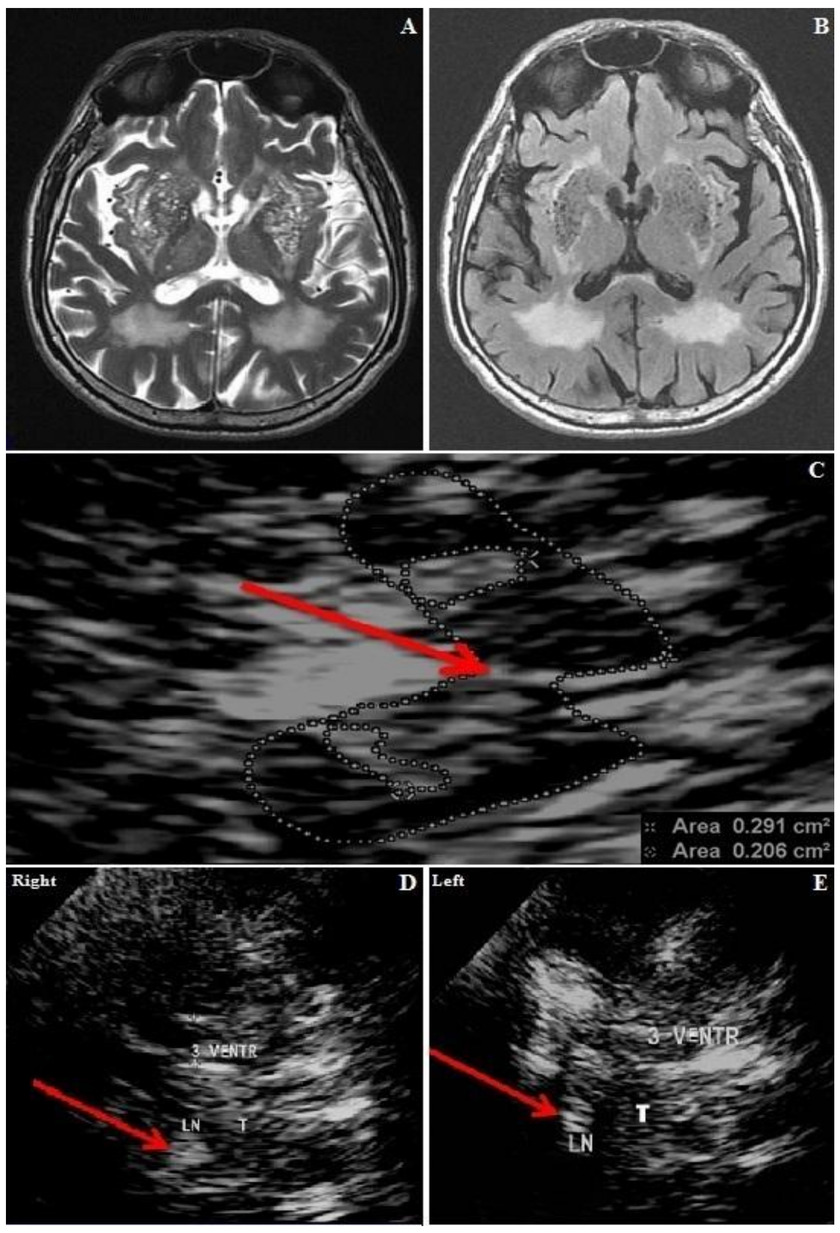

Figure 1. *Neuroradiological and transcranial sonographic study in twin A.*
A-B: FLAIR and T2-weighted brain MRI images show neuroimaging features of CADASIL with confluent lesions in the external capsule and in the subcortical white matter of the frontal and temporal lobes. Vascular lesion is present in the right anterior limb of internal capsule. MRI shows also a marked cribriform state of lenticular and caudate nucleus due to lenticulostriate perivascular spaces dilation. *C*: Through a transtemporal right approach, the TCS image shows enlarged right and left substantia nigra hyperechogenicity (right 0,29 cm2; left 0.20 cm2); the midline raphe (red arrow) appears normoechogenic and not interrupted. *D-E*: Through a transtemporal bilateral approach, TCS images show bilateral hyperechogenicity of lenticular nucleus (LN – red arrows) and slight increase of the 3° Ventricle (3VENTR) width (T: Thalamus).

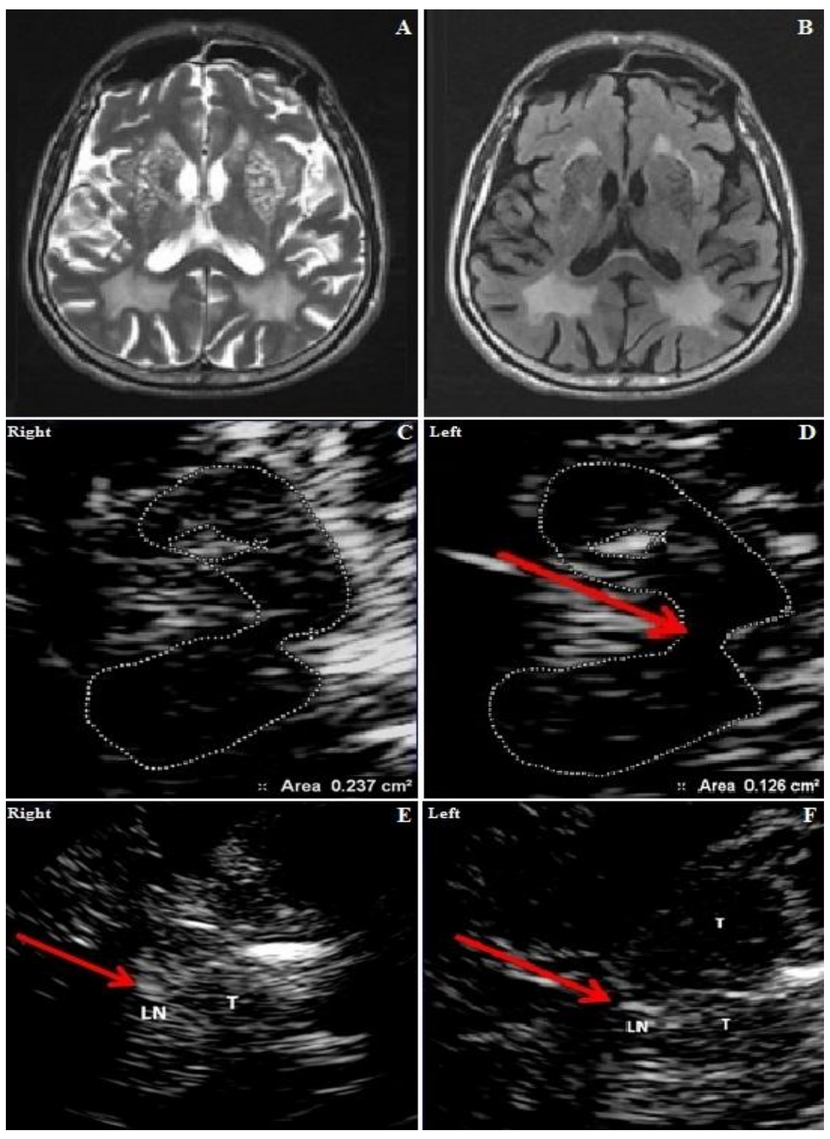

Figure 2. *Neuroradiological and transcranial sonographic study in twin B.*
A-B: FLAIR and T2-weighted brain MRI images show a pattern of lesions distribution similar to that of twin A: typical white matter changes of CADASIL, lacunar infarction involving the right anterior limb of internal capsule and cribriform state of putamen, pallidum and caudate nuclei. *C-D*: Through a transtemporal bilateral approach, TCS images show enlarged right substantia nigra hyperechogenicity (0,23 cm2) and left substantia nigra hyperechogenicity within normal range with interruption of the midline raphe (red arrow). *E-F*: Through a transtemporal bilateral approach, TCS images show bilateral hyperechogenicity of lenticular nucleus (LN - red arrows) and slight increase of the 3° Ventricle width (T: Thalamus).

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