Amyotrophic Lateral Sclerosis as a clinical presentation of LRRK2 mutations?

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***Objective*: to evaluate clinical spectrum of LRRK2 by studying a family with different clinical phenotypes across its members.**

Materials: a 72 year-old man presented at our Clinic with one year history of progressive weakness of the left limbs, walking impairment and lack of accuracy in arm movement. He later developed bradykinesia, muscolar cramps, fasciculations, dysphagia and dysarthria. At neurological examination he presented hypomimia and bradykinesia, and increased muscolar tone at lower and upper limbs which showed also distal weakness. Tetrahyperreflexia was present. Patient's uncle and three cousins (paternal line) had all a diagnosis of PD (Fig 1).

Methods: Patient performed brain MRI (chronic vascular encephalopathy) and FP-CIT SPECT which showed a bilateral nigro-putaminal degeneration. Electromyography exhibited denervation and fasciculations in upper and lower limbs (but not in cranial district) and Motor Evoked Potentials were consistent with upper motor neuron involvement in all limbs. CSF was normal.

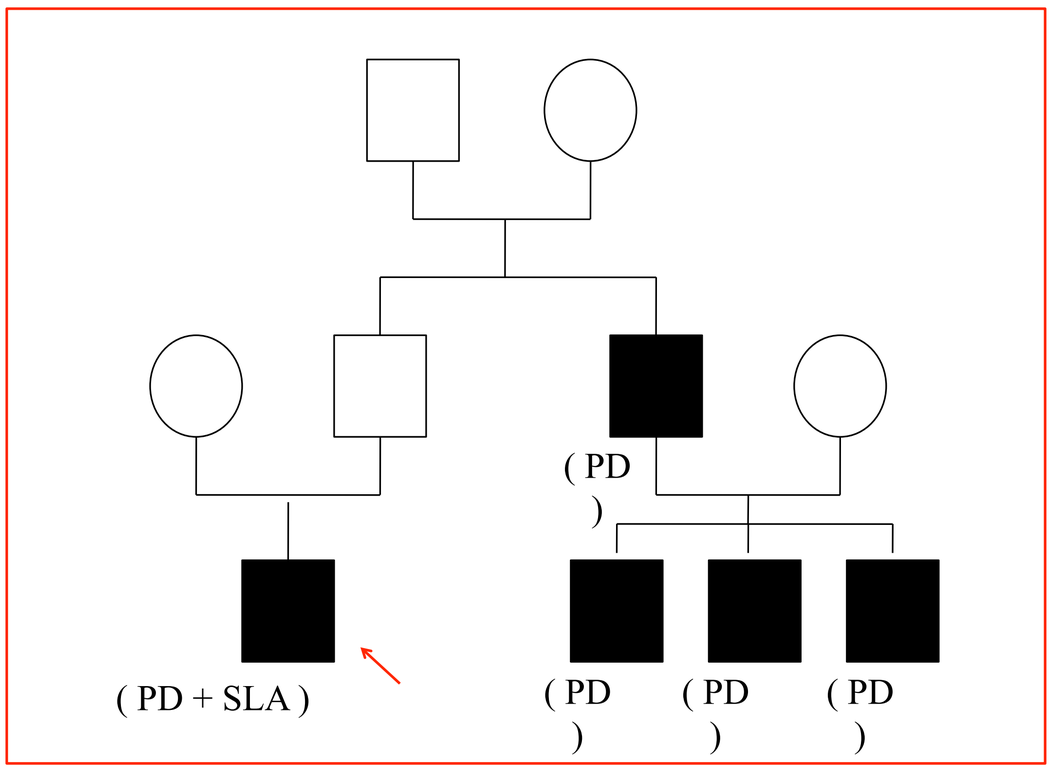

Fig. 1. Family tree. In brackets the clinical phenotype of affected patient. Red arrow shows proband.

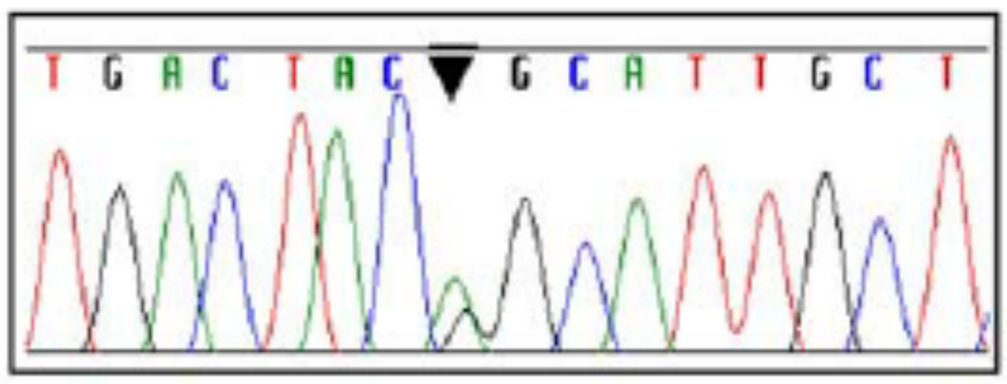

Fig 2. Sequence analysis of the exon 41 of the LRRK2 gene.

Results: A diagnosis of Motor Neuron Disease and PD was done to our patient. Taking account into his family history for PD, we looked-for LRRK2 mutations. G2019S mutation was found both in our patient and in all his cousins. SOD1 mutations were excluded.

***Discussion*:** Leucine-Rich Repeat Kinase 2 (LRRK2) mutations are the most common in Parkinson's disease (PD). They are thought to produce a clinical phenotype almost indistinguishable from idiopathic PD[1]. However isolated cases of frontotemporal dementia, Corticobasal Syndrome, Primary Progressive Aphasia have been reported in LRRK2-mutation and in 1997 limb muscle weakness, atrophy and fasciculations were described in two affected members of a large German-Canadian family presenting LRRK2 mutation[2]. Following studies failed to reveal LRRK2 mutations in ALS patients[3] even when they exhibited extrapyramidal signs. More recently an ALS patient with extrapyramidal signs and positive FP-CIT SPECT showed LRRK2 mutation, but a coincidental association could not be ruled out.

***Conclusions*: although the most frequent phenotype of LRRK2 mutations is represented by PD, LRRK2 phenotypic spectrum is broader than expected, consistent with its pleomorphic histopathology. Thus in our opinion LRRK2 mutations should be ruled out in all families presenting with many affected members and high variability in phenotype.**

References

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