C9ORF72 gene expansion in a case of intellectual disability and late-onset neurodegeneration

A R Pati[1], C Battisti[1], S Battistini[1], A Trapassi[2], R Marconi[3], A Mignarri[1], A Federico[1]and MT Dotti[1].

[1]Department of Medicine, Surgery and Neurosciences. University of Siena, Siena, Italy
[2]Neurology Service, Azienda Sanitaria Locale 7 Siena, Siena, Italy
[3]Unit of Neurology, Ospedale della Misericordia Grosseto, Grosseto, Italy

Background

The expansion of the hexanucleotide *GGGGCC* in the first intron of chromosome 9 open reading frame 72 (*C9ORF72*) is related to different clinical phenotypes including frontotemporal dementia (FTD), motor neuron disease (MND), and rarely psychiatric symptoms or movement disorders.

Case report

A 67 year-old woman with a history of mild mental retardation until adolescence presented a nine-month history of rapid motor and cognitive impairment. Her mother had the same phenotype, characterized by mental retardation and rapidly progressive dementia at age 60; an uncle had been treated for psychiatric disease and the grandfather had mental retardation.

•Neurological examination: emotional lability, anartria and spasticity of the four limbs.

•At brain CT-scan: diffuse cortical-subcortical atrophy.

•Cerebrospinal fluid examination showed low levels of Amyloid-β_1-42 (284 pg/ml, n.v. >600) with normal Total Tau (160 pg/ml, n.v. <275) and Phosforylated-Tau (18 pg/ml n.v. <50).

•Molecular analysis of ***C9ORF72* revealed a pathogenetic expansion (> 45 GGGGCC repeats, cut-off 30 repeats).**

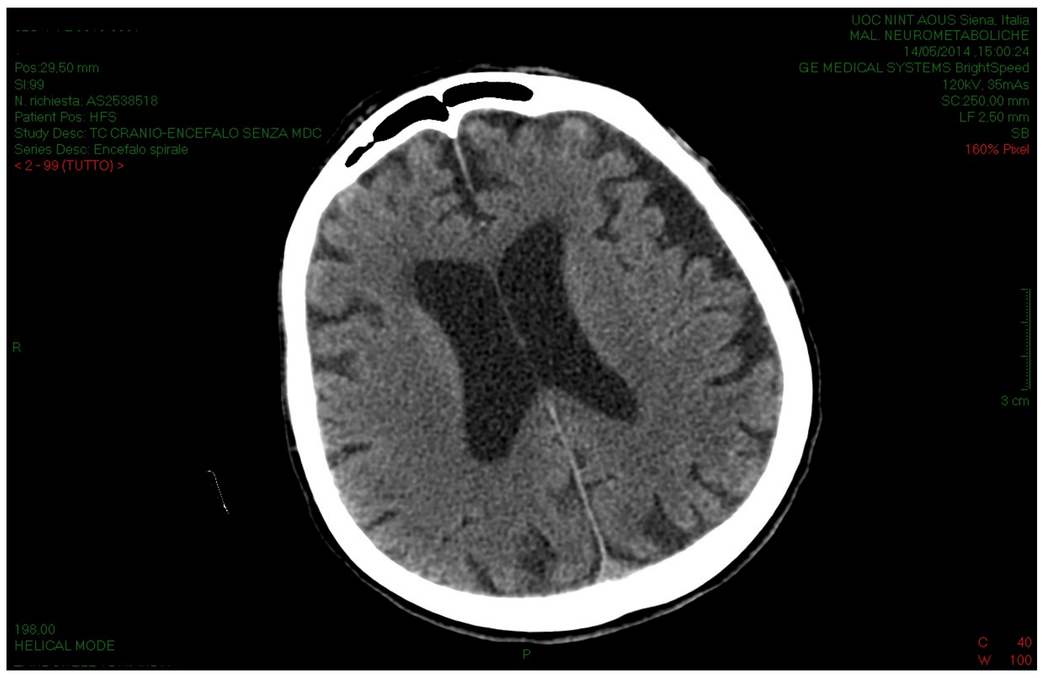


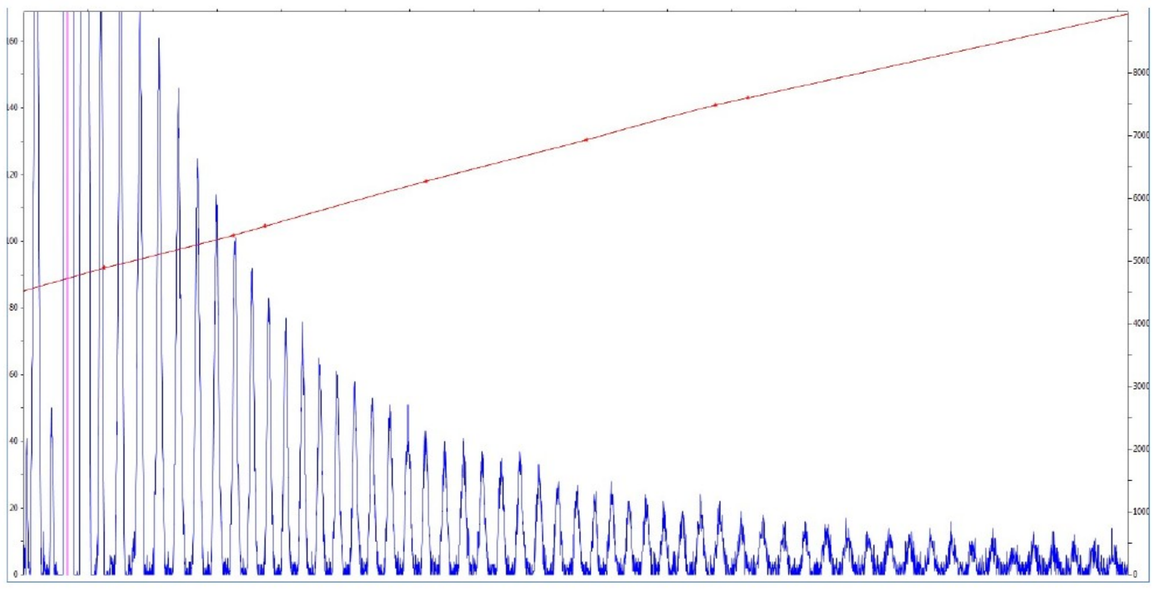
Figure legend: Brain TC scan: atrophy and ventricles enlargement

Conclusion

Patients with *C9ORF72* expansion can present with variable clinical phenotypes. Intellectual disability in C9ORF72-mutated patients has been previously described only in two members of a single family subsequently presenting FTD. Our case further suggests a possible link between intellectual disability and *C9ORF72* gene mutation.

It could be useful to perform *C9ORF72* analysis in patients affected by intellectual disability with familiar history of psychiatric disorders and/or FTD

Repeat-primed PCR results of the patient with hexanucleotide expansion showing the typical saw-tooth pattern.



The presence of the expanded hexanucleotide repeat and the number of repeat units in the longest allele was determined using previously reported methods for repeat-primed PCR and fluorescence-based fragment size analysis (Renton, 2011). Briefly, repeat-primed PCR was performed in a total reaction volume of 28 µl containing 150 ng genomic DNA, 1× FastStart PCR Master Mix (Roche Applied Science, Indianapolis, IN, USA), 3.5% DMSO, 1× Q solution (Quiagen, Valencia, CA) and 0.18 mM of deazaGTP (NEB, Ipswich, MA). Primer concentrations and sequences (chr9:27563580F and chr9:27563465R) were the same as previously reported (Renton, 2011). PCR products were run on an ABI® 3130 XL Genetic Analyzer (Applied Biosystems) and analyzed using GeneMapper®. Consistent with standards used in prior studies, a sample was considered to have a repeat expansion when assay replicates demonstrated >30 peaks and a decrementing saw-tooth pattern.

References

1. Liu Y, Yu JT, Zong Y, Zhou J, *Tan L, C9ORF72 Mutations in Neurodegenerative Diseases,* Molecular Neurobiology (2014) volume 49, Issue 1,6-398
2.Snowden JS, Rollinson S, Thompson JC, Harris JM, Stopford CL, Richardson AM, Jones M, Gerhard A, Davidson YS, Robinson A, Gibbons L, Hu Q, DuPlessis D, Neary D, Mann DM and Pickering-Brown SM, *Distinct clinical and pathological characteristics of frontotemporal dementia associated with C9ORF72 mutations*, doi:10.1093/brain/awr355 Brain (2012): 135; 693–708
3.Proudfoot M, Gutowski NJ, Edbauer D, Hilton DA, Stephens M, Rankin J, Mackenzie IR, *Early dipeptide repeat pathology in a frontotemporal dementia kindred with C9ORF72 mutation and intellectual disability*, Acta Neuropathol (2014) 127:451–458 DOI 10.1007/s00401-014-1245-7

Sin
XLVII CONGRESSO NAZIONALE
22-25 OTTOBRE 2016 – VENEZIA
WebPoster