MIGHT INTERMEDIATE ALLELES IN THE *HTT* GENE BE PATHOGENIC?

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BACKGROUND

Intermediate Alleles (IAs) are expansions of CAG repeats in the *HTT* gene between 27 and 35 repeats. The frequency of IAs in the general population varies considerably among populations. IAs are known to be instable, being able to expand into the pathologic range in descents of carriers. Beyond that, the clinical meaning of IAs is controversial for several reasons:

1. Huntington's disease (HD) can be easily misdiagnosed with other neurodegenerative diseases, particularly when the number of CAG repeats is in the lower pathological range[1].
2. Studies report a higher risk of cognitive and motor impairment in carriers of IAs[2].
3. A number of carriers of IAs have been diagnosed with HD[3-7]. However, few of these cases have neuropathological confirmation[8].

Here we report our series of cases where Huntington's was suspected and the number of CAG repeats in the *HTT* gene was found to be in the intermediate range.

METHODS

First, we screened the number of CAG repeats in the *HTT* gene in a cohort of > 500 healthy subjects in order to find out the relative frequency of IAs among controls in our population. We also calculated the frequency of IA in patients diagnosed with HD (CAG repeats in the pathologic range in one chromosome and in the intermediate range in the other one).
Then, we selected from our databases all cases where clinicians suspected Huntington's disease and the number of CAG repeats in the *HTT* gene was found to be between 27 and 35 in any of the two chromosomes but ≤ 35 repeats in both of them. We ruled out and cases with putative alternative diagnosis and cases with familial antecedents of Huntington's disease.
Finally, we revised the clinical records of all cases to collect their age at onset, signs, symptoms, and neuroimaging findings.

RESULTS

The relative frequency of IAs among controls in our healthy population is 2.9%.
The relative frequency of IAs among our patients with HD (CAG repeats in the pathologic range in one chromosome and CAG repeats in the intermediate range in the other) is 7.4%.
In our series, the relative frequency of IAs among cases where HD is suspected but none of the chromosomes has ≥ 36 repeats is 8.8%.

RESULTS

We identified 8 cases with Huntington's phenotype being carriers of IAs in the *HTT* gene (5 males and 3 females). Mean age at onset was 64 years old (range 43-85).
Clinical pictures included a variable combination of motor, cognitive and neuropsychiatric symptoms. Among motor symptoms dystonia was the most frequent one (75%), followed by chorea (62.5%), myoclonus (25%) and tremor (12.5%). Among neuropsychiatric symptoms, depression was the most frequent one (62.5%), followed by control impulse disorders (37.5%), psychotic symptoms (25%) and apathy (12.5%). The only cognitive symptom was memory complaints, present in 37.5%.
CT and MRI scans were normal but two cases with mild small vessel disease and one with iron deposits in basal ganglia; although mild, diffuse cortical atrophy was observed in all cases. One of the cases had a normal DaT-SPECT; and another case with 30 CAG repeats had an abnormal FDG-PET scan with hypometabolism in both caudate nuclei, thalami, and frontal cortex (Figure 1).

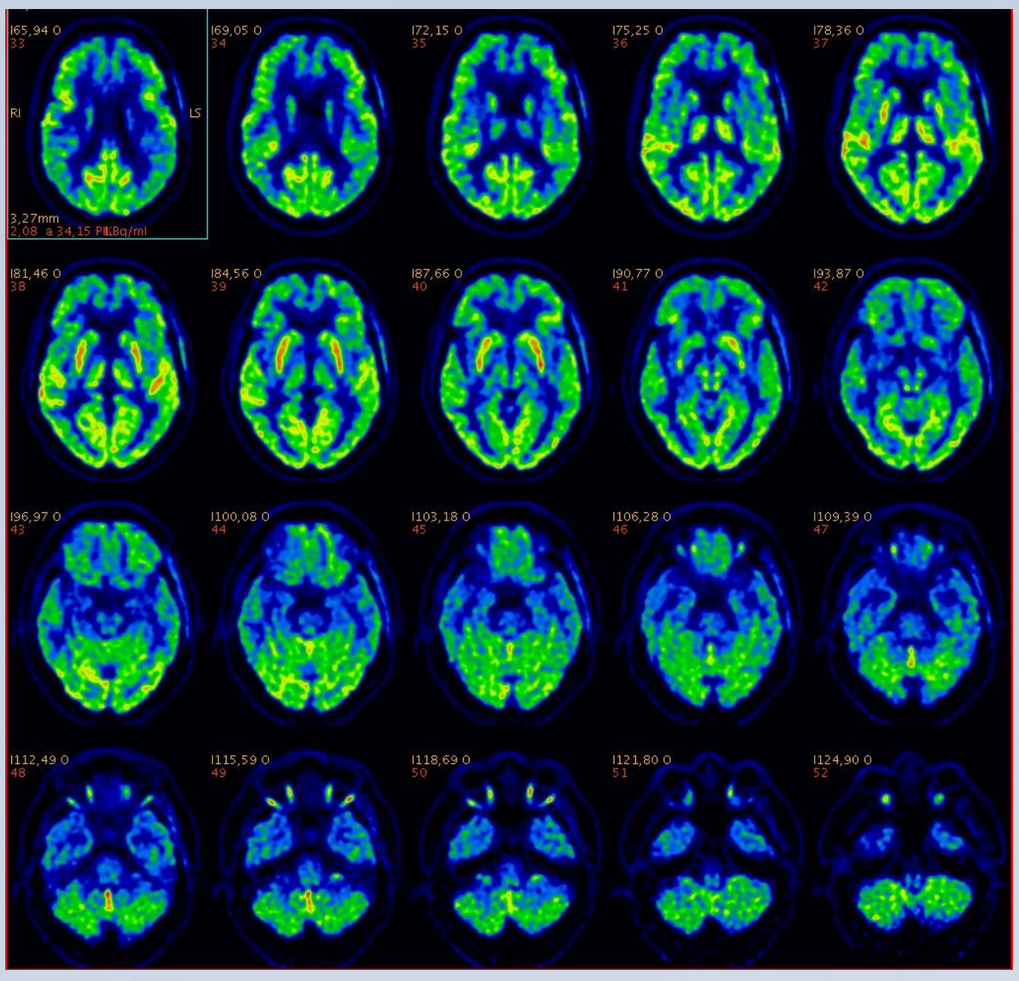

Figure 1. FDG-PET of 69 years old man with 30 CAG repeats.

CONCLUSIONS

- Up to our knowledge, this is the larger series of cases with Huntington's phenotype in carriers of IAs in the *HTT* gene.
- The frequency of IAs is higher in patients with Huntington's phenotype than in controls.
- However, none of our cases has neuropathological study, therefore the causative effect can not be determined.
- Larger series and neuropathological studies are needed to confirm or rule out whether IAs in the *HTT* may cause Huntington's disease.

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