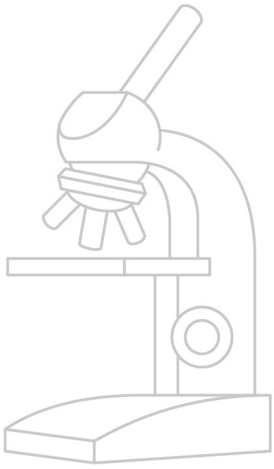
# Juvenile Huntington Disease: towards better understanding its unique disease characteristics

Bakels, H.S.



CHAPTER 5

# Post-mortem 7T MR imaging and neuropathology in middle stage juvenile-onset Huntington Disease: a case report

Hannah S. Bakels, Sjoerd G. van Duinen, Jeroen de Bresser, Willeke M.C. van Roon-Mom, Louise van der Weerd and Susanne T. de Bot

*Published as: Bakels HS, van Duinen SG, de Bresser J, van Roon-Mom WMC, van der Weerd L, de Bot ST. Post-mortem 7T MR imaging and neuropathology in middle stage juvenile-onset Huntington disease: A case report. Neuropathol Appl Neurobiol. 2023 Feb;49(1):e12858.*

## INTRODUCTION

Huntington disease (HD) is an autosomal dominant inherited brain disorder, caused by an elongated CAG-repeat in the HTT gene. It typically manifests during adulthood, but in approximately 5% of cases, the disease occurs in minors, referred to as juvenile-onset HD (JHD). [1] JHD patients have a distinct clinical presentation often with early cognitive changes, Parkinsonism and epilepsy in patients with childhood-onset and early cognitive and psychiatric disturbances in adolescent-onset disease. [2] , [3] HD neuropathology is characterised by atrophy, as revealed by a reduction in brain volume, neuronal cell loss and reactive changes in astro and oligodendroglia. These changes are most prominent in the neostriatum (e.g. caudate nucleus and putamen), following a caudorostral gradient with disease progression but extend to other brain regions (e.g. globus pallidus, [hypo]thalamus, cortex, brain stem and cerebellum) as well. Neostriatal findings are formulated in the fivescale Vonsattel grading system, [4] a measure of neuropathological severity. Endstage neuropathology in JHD cases is generally more severe than in adult-onset cases. [3] , [5] Reductions in brain volume and in the volume of specified regions are also apparent in in vivo imaging studies in HD patients, [6] yet a comparison of postmortem imaging and neuropathological findings at the same time point in the same patient is lacking. Furthermore, the majority of postmortem studies are performed on endstage disease. Therefore, an exploration of the relationship between early clinical characteristics and neuropathological grading in HD brain donors who died after a short disease duration has not been undertaken. Here, we report a case study of a JHD brain donor with a moderate clinical disease burden and short clinical disease duration. Ex vivo, in situ ultrahigh field 7T MR imaging revealed bilateral atrophy of the neostriatum, most significantly of the putamen. Neuropathological assessment revealed sparse neuronal loss and limited gliosis of the same regions, in keeping with Vonsattel grade 1. This case report highlights the risk of underestimating neuropathological severity by Vonsattel grading, due to undervaluation of neuropathological changes outside the head of the caudate nucleus (HCN). Atrophy of the putamen was pronounced in this case; therefore, the entirety of the neuropathological findings should always be taken into account in HD brain donors that did not reach endstage disease. Studies like these increase our understanding of how early clinical disease characteristics and imaging are related to neuropathological changes and grading and vice versa.

### Clinical characteristics

The patient was a man who died at 21 years of age by legally approved euthanasia. He was clinically diagnosed with HD at 19 years of age, therefore referred to as juvenile (adolescent) onset HD. [2] , [3] Molecular analysis of the *HTT* gene revealed a pathologically expanded CAG-repeat of 57. The earliest symptom of his disease was learning difficulty and this developed 2 years before diagnosis. The patient had a moderate clinical disease burden shortly before death. Clinical characteristics included moderate/common generalised chorea and truncal dystonia, ataxia, balance disorder, mild dysarthria, dysphagia, mild dysexecutive disorder and frequent irritative and aggressive outbursts. Clinical Global Impression of Severity was scored from 4 to 5 on a 7point scale (e.g. 1; not at all ill to 7; extremely ill). [7] Functional disabilities were mild to moderate, including the inability to work, and needing assistance in domestic chores. Patient independence was scored as stage 2 using the Shoulson–Fahn ranking system and a total functional capacity of 6. [8] The short disease duration of 4 years was paralleled by a moderate CAGAge Product score of 490, a measure of disease progression. [9]

## METHODS

The patient and his relatives gave informed consent for brain autopsy, postmortem MRI and the pseudonymized use of clinical characteristics and brain tissue for research purposes and publication. The study followed the tenants of the Declaration of Helsinki. Ex vivo, in situ ultrahigh field 7T MR brain imaging was performed within 3 h postmortem delay (PMD) and brain autopsy and dissection within 11 h PMD. Brain dissection was performed following a standard protocol. [10]

## RESULTS

By radiological assessment, the donor had severe bilateral atrophy of the putamen and slight to moderate atrophy of the HCN, which was best appreciated at the dorsal side of the caudate head (Figure 1A,C). We could not reliably determine if there was atrophy in the body and tail of the caudate nucleus due to their small size, and therefore, we could not confidently determine if there was a gradient in the caudate nucleus degeneration. There were no signs of atrophy outside the neostriatum.

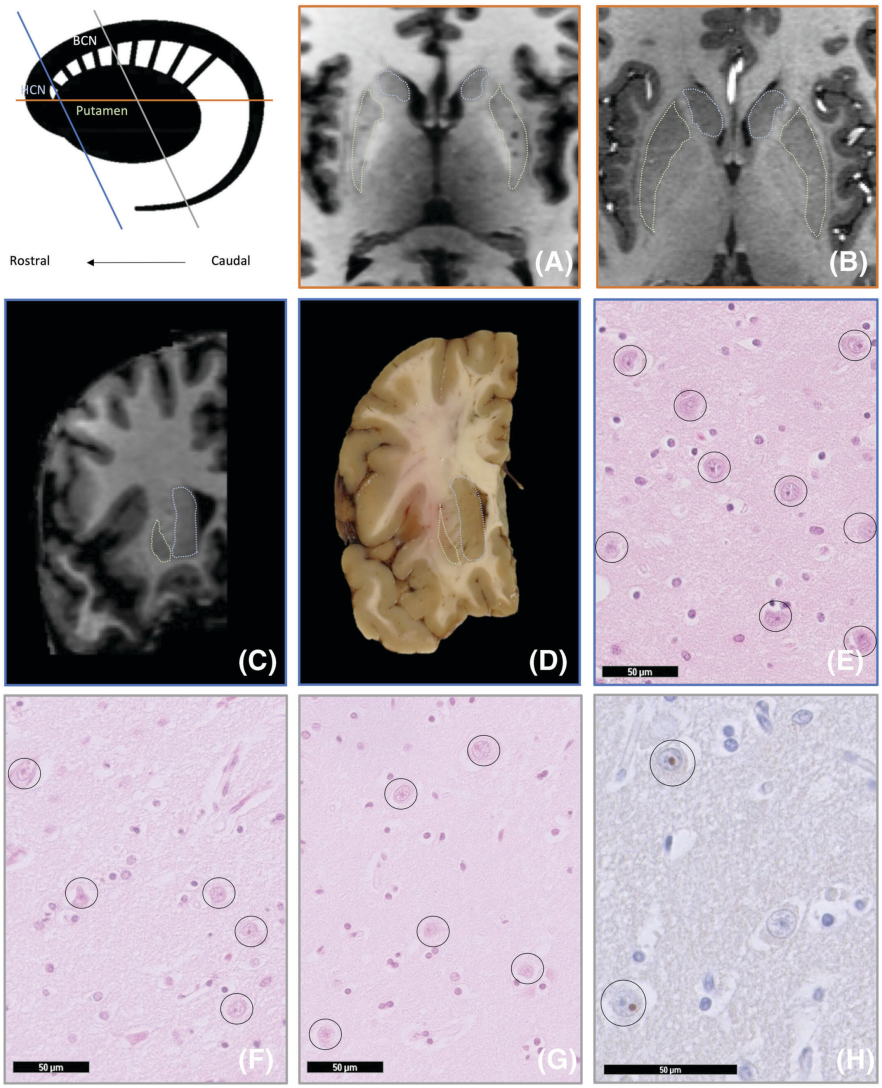



**Figure 1.** Postmortem 7T MRI imaging and neuropathology of a juvenile-onset Huntington disease (HD) brain donor.

T1weighted image in a transverse plane of the HD brain donor (A) demonstrates severe bilateral atrophy of the putamen (dashed green line) and slight to moderate atrophy of the HCN (dashed blue line) as compared to an age and sexmatched control (B). T1weighted image in the coronal plane of the HD brain donor (C) parallels neuropathology macroscopy findings of the right hemisphere of the same HD donor (D), demonstrating a normal convex contour of the HCN into the lateral ventricle (right side of the dashed blue line) and moderate to severe atrophy of the putamen (dashed green line). H&E staining of the HCN (E) and rostral putamen (not shown) reveals normal neuronal cellularity (circles) and no signs of gliosis. Microscopy of the BCN (F) and caudal putamen (G) reveals mild neuronal loss (fewer circles) and gliosis. Mutant–Huntingtin staining (H) reveals scattered nuclear immunoreactivity (circles) of neurons in the BCN, similar to neurons in the frontal lobe and putamen (not shown). Legend: BCN, body of caudate nucleus; HCN, head of caudate nucleus; H&E, haematoxylin and eosin

By brain autopsy, gross brain weight was 1480 g (normal for this age and sex). The neuropathological assessment revealed no macroscopic evidence of atrophy with a normal contour of the HCN into the lateral ventricles (Figure 1D). Microscopically, the HCN and rostral putamen revealed a normal density of neuronal cell bodies and no signs of astrogliosis (Figure 1E). In the body of the caudate nucleus (BCN; at height of the anterior thalamus), there was a minor loss of neurones and gliosis (Figure 1F). We were not able to microscopically assess the tail of the caudate nucleus in the histopathological sections that were available. Neuronal loss was most prominent in the caudal putamen, including a mild degree of gliosis (Figure 1G). These findings are consistent with a Vonsattel grade 1. Cell distribution and morphology in other striatal and cortical regions appeared normal. Immunohistochemistry for mutantHuntingtin revealed scattered nuclear aggregates in neurons of the frontal lobe, caudate nucleus and putamen (Figure 1H).

## DISCUSSION

Several conclusions can be drawn from this illustrative case report. This patient had a characteristic adolescent-onset HD presentation with cognitive onset of disease, severe psychiatric disturbances and a motor phenotype including ataxia, dystonia and chorea. This moderate disease burden, combined with mild to moderate functional disability and short disease duration, is paralleled by mild neuronal cell loss and gliosis of the neostriatum, which was most prominent in the caudal putamen, without evident cell loss and gliosis in other brain regions. More prominent atrophy of the putamen, as compared with the caudate nucleus, in early HD stages, has been mentioned in the literature before. [11] The discrepancy between moderate disease burden and mild neuropathology most likely relates to the notion that disease burden is primarily caused by neuronal dysfunction and only secondary by neuronal loss. [12] Furthermore, the presence of neuronal mHTT aggregates in our donor with a relatively high CAG-repeat length, and short disease duration is in line with former studies revealing mHTT aggregates even in presymptomatic HD brain donors and correlating with CAG-repeat length. [13] , [14] Severe macroscopic atrophy of the putamen was best appreciated via imaging and confirmed by the microscopic finding that the most prominent neuronal cell loss and reactive gliosis was in this region. Neuropathology in the putamen followed a caudalrostral gradient with the most severe neuronal loss in the caudal putamen, at the level of the thalamus and less neuronal change in the rostral putamen at the level of the nucleus accumbens. This case highlights possible undervaluation of neuropathological severity since

Vonsattel grading is mostly defined by macroscopic volume loss of the HCN (rostral neostriatum) in the lateral ventricle, a change that is usually appreciated only in later stages of the disease. Consideration of macroscopic atrophy of the putamen on coronal sectioning, particularly in HD donors that have not progressed to endstage disease, is therefore warranted. Further multimodal (i.e., clinical, functional, imaging and neuropathology) studies are needed in HD brain donors with relatively short disease duration, in order to improve understanding of how various HD measures relate to one and another and to improve the use of diagnostic, grading and staging criteria in HD.

## REFERENCES


1. Quarrell O, O'Donovan KL, Bandmann O, Strong M. The prevalence of juvenile Huntington's disease: a review of the literature and metaanalysis. PLoS Curr. 2012;4:e4f8606b742ef3. doi: 10.1371/4f8606b742ef3
2. Fusilli C, Migliore S, Mazza T, et al. Biological and clinical manifestations of juvenile Huntington's disease: a retrospective analysis. Lancet Neurol. Nov 2018;17(11):986993. doi: 10.1016/s1474-4422(18)30294-1
3. Bakels HS, Roos RAC, van Roon-Mom WMC, de Bot ST. Juvenile-onset Huntington disease pathophysiology and neurodevelopment: a review. Mov Disord. 2022;37(1):1624. doi: 10.1002/mds.28823
4. Vonsattel JP, Myers RH, Stevens TJ, Ferrante RJ, Bird ED, Richardson EP Jr. Neuropathological classification of Huntington's disease. J Neuropathol Exp Neurol. Nov 1985;44(6):559577. doi: 10.1097/00005072-198511000-00003
5. Vonsattel JP, Keller C, Cortes Ramirez EP. Huntington's disease neuropathology. Handb Clin Neurol. 2011;100:83100. doi: 10.1016/b978-0-444-52014-2.00004-5
6. Kinnunen KM, Schwarz AJ, Turner EC, et al. Volumetric MRIbased biomarkers in Huntington's disease: an evidentiary review. Front Neurol. 2021;12:712555. doi: 10.3389/fneur.2021.712555
7. Busner J, Targum SD. The clinical global impressions scale: applying a research tool in clinical practice. Psychiatry (Edgmont). 2007;4(7):2837.
8. Shoulson I, Fahn S. Huntington disease: clinical care and evaluation. Neurology. 1979;29(1):13. doi: 10.1212/wnl.29.1.1
9. Zhang Y, Long JD, Mills JA, Warner JH, Lu W, Paulsen JS. Indexing disease progression at study entry with individuals atrisk for Huntington disease. Am J Med Genet. 2011;156b(7):751763. doi: 10.1002/ajmg.b.31232
10. Waldvogel HJ, Bullock JY, Synek BJ, Curtis MA, van RoonMom WM, Faull RL. The collection and processing of human brain tissue for research. Cell Tissue Bank. 2008;9(3):169179. doi: 10.1007/s10561-008-9068-1
11. Harris GJ, Pearlson GD, Peyser CE, et al. Putamen volume reduction on magnetic resonance imaging exceeds caudate changes in mild Huntington's disease. Ann Neurol. Jan 1992;31(1):6975. doi: 10.1002/ana.410310113
12. Ross CA, Tabrizi SJ. Huntington's disease: from molecular pathogenesis to clinical treatment. Lancet Neurol. Jan 2011;10(1):8398. doi: 10.1016/s1474-4422(10)70245-3
13. GomezTortosa E, MacDonald ME, Friend JC, et al. Quantitative neuropathological changes in presymptomatic Huntington's disease. Ann Neurol. 2001;49(1):2934. doi:
14. Hickman RA, Faust PL, Marder K, Yamamoto A, Vonsattel JP. The distribution and density of huntingtin inclusions across the Huntington disease neocortex: regional correlations with huntingtin repeat expansion independent of pathologic grade. Acta Neuropathol Commun. 2022;10(1):55. doi: 10.1186/s40478-022-01364-1