Main title

A case of TDP-43 type C pathology presenting as nonfluent variant primary progressive aphasia

Running head (<50 characters)

A case of nfvPPA with TDP-43 type C pathology

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Number of words: abstract 250, main body 2936; Figures 3; Tables 1.

Disclosure of interest

The authors report no conflict of interest.

Abstract

We report a case of rapidly progressive nonfluent variant PPA (nfvPPA), age at onset 77 years old and disease duration 3.3 years, who came to post mortem and was found to have TDP-43 type C pathology, an unusual finding for nfvPPA. Clinical features were in keeping with consensus criteria for nfvPPA but magnetic resonance imaging (MRI) was atypical, with marked left temporal lobe atrophy as well as features characteristic of nfvPPA (left inferior frontal and insula atrophy). All prior TDP-43 type C cases from the UCL FTD cohort (n=25) had a semantic variant PPA (svPPA) phenotype, with all having a younger age at onset and longer disease duration than the nfvPPA case. Volumetric analysis of MRI scans from the nfvPPA case, twelve of the svPPA cases and ten age-matched controls was performed. Whilst left frontal and insular volumes were lower in the nfvPPA case compared with svPPA (e.g. left dorsolateral prefrontal cortex 78% of control mean value versus 96%), cortical and medial temporal lobe volumes were lower in the svPPA group compared with the nfvPPA patient. This was the case to a small extent in the left hemisphere but was particularly marked in the right hemisphere (e.g. left amygdala – svPPA 61% of controls, nfvPPA 66%; right amygdala – svPPA 79%, nfvPPA 93%). Such anatomical involvement is likely to be consistent with the presence of a nonfluent aphasia (left frontal lobe and insula), and only mild semantic deficit early in the illness (left but not right temporal lobe). Such unique cases add to the heterogeneity of the FTD spectrum.

Keywords: frontotemporal dementia, nfvPPA, svPPA, TDP-43, nonfluent variant, semantic variant, primary progressive aphasia, pathology, MRI

Introduction

In 2006, the protein transactive response DNA binding protein 43kDa (TDP-43) was found to be implicated in the pathogenesis of frontotemporal dementia (FTD) (Neumann et al, 2006). It was subsequently shown that inclusions of abnormally phosphorylated TDP-43 are the most common pathological form of FTD, with four main subtypes recognised (named types A, B, C and D in the harmonized classification: Mackenzie et al, 2011). Unlike the other forms of TDP-43 pathology, type C appears to be a sporadic disease, and clinically, has been associated most closely with semantic variant primary progressive aphasia (svPPA, also known as semantic dementia) (Rohrer et al, 2011; Bergeron et al, 2018). In contrast, nonfluent variant PPA (nfvPPA) is usually a tauopathy, and when it is associated with TDP-43 pathology it is usually the type A subtype. In a recent meta-analysis of pathological causes of PPA, 99% of cases of TDP-43 type C had an svPPA phenotype, with no cases of nfvPPA caused by this TDP-43 subtype (Bergeron et al, 2018). Here, we describe the clinical, imaging and pathological features of nfvPPA associated with TDP-43 type C.

Clinical details

History and examination

A 77-year-old right-handed woman presented with progressive speech production difficulty. Her symptoms began two years earlier, with stuttering and halting, effortful speech. She made frequent binary reversals, often saying yes when she meant no, and vice versa. However, her understanding remained intact, and she never asked the meaning of a word. She would at times write agrammatical sentences with missing function words. Over the following two years she rapidly deteriorated to the extent that her speech output was restricted to one word

– ‘definitely’ – which she enunciated with difficulty. However she was still able to point to items to help with communication, suggesting more intact comprehension. She had frequent laughter-like vocalisations in lieu of verbal output. Whilst she developed altered appetite with a sweet tooth late in her illness, other behavioural changes were not present. Physically, she had had a worsening right upper limb tremor for at least five years preceding her speech problems with progressive difficulty using that arm to hold cutlery or write – this was diagnosed initially as an essential tremor.

She had no significant past medical history and was not on any medication. There was a family history of late onset Parkinson’s disease affecting her mother, maternal aunt and maternal grandmother.

On examination she had a normal social façade and demonstrated appropriate empathy. She had severe motor speech impairment and was unable to repeat even monosyllabic words, making cognitive examination difficult. Despite this she was able to understand single words of both high and medium frequency on a word-picture naming task, although difficulties were present with low frequency words. She was able to demonstrate object use e.g. a comb and mug. Furthermore, she was able to identify famous faces (e.g. the current prime minister) through pointing. In terms of other cognitive domains, executive function was also impaired.

Physical examination revealed a no-no head tremor and orofacial apraxia. Eye movements and bulbar examination were normal. In the limbs there was a postural right upper limb tremor, with increased tone and cogwheeling and limb apraxia in both upper limbs. There

was no evidence of upper or lower motor neurone involvement on examination and her swallow assessment was normal.

Magnetic resonance imaging

An MRI scan of her brain revealed marked asymmetrical atrophy predominantly affecting the left hemisphere (Figure 1, left hand column). There was significant atrophy of the left inferior frontal lobe and insula, as well as the left anterior temporal lobe, with profound 'knife-edge' atrophy of the temporal pole.

(FIGURE 1 about here)

Diagnosis

The clinical features were most in keeping with nfvPPA given the early halting, effortful speech and agrammatism, and inability to understand complex commands (Gorno-Tempini et al, 2011). However, although single-word comprehension and object knowledge seemed *relatively* spared there was evidence of deficits on more difficult semantic tasks e.g knowledge of low-frequency words. From an imaging perspective, posterior fronto-insula atrophy was consistent with a diagnosis of nfvPPA, however the striking and predominant left temporal lobe atrophy was felt to be unusual.

Genetics

A next generation sequencing panel for mutations in seventeen genes associated with dementia (including *MAPT* and *GRN*) was negative (Koriath et al, 2018) as was testing for *C9orf72* expansions.

Clinical progress

Her symptoms continued to rapidly progress and she died a year later, three years and four months after symptom onset.

Pathology

She donated her brain to the Queen Square Brain Bank for Neurological Disorders (QSBB). The brain weighed 1502g, and macroscopically there was marked atrophy of the frontal lobe, anterior temporal lobe, hippocampus and amygdala. The right hemisphere was frozen at -80°C and the left hemisphere was fixed in formalin then coronally sliced and representative blocks removed and processed into wax blocks. The standard QSBB pathological protocol was used on the fixed blocks with representative areas of neocortex (superior and inferior frontal [including Broca's area], temporal [at the level of the mamillary body], parietal and occipital), basal ganglia, hippocampus, midbrain, pons, medulla and cerebellum examined using routine immunohistochemical staining for Aβ, tau (AT8), TDP-43, ubiquitin, p62, and α-synuclein.

Histological examination revealed abundant TDP-43 positive dystrophic neurites which were long and corkscrew in shape along with sparse neuronal cytoplasmic inclusions within the frontal and temporal lobes as well as the caudate and putamen. The hippocampus showed severe neuronal loss and gliosis in the subiculum and sparse TDP-43 positive neuronal cytoplasmic inclusions in the dentate fascia. This corresponds to the type C subtype of TDP-43 pathology (Figure 2). Tau pathology in the form of neurofibrillary tangles and threads corresponded to Braak and Braak stage II. No Aβ deposition was observed in any of the areas

tested, and no α-synuclein pathology was present in the hippocampus, amygdala, or brainstem. The Xth and XIIth cranial nerve nuclei were well preserved, and examination of the spinal cord at cervical and three thoracic levels showed no abnormality on routine staining.

(FIGURE 2 about here)

Comparison with other cases with TDP-43 type C pathology in the UCL FTD cohort (Table 1)

Following the unusual finding of TDP-43 type C pathology we reviewed the University College London FTD database to find other patients who had come to postmortem and had the same pathology. Of the 25 other patients, all had a diagnosis of svPPA all with characteristic features of impaired semantic knowledge, fluent aphasia and single word comprehension difficulties. None of the others had motor impairment, either amyotophic lateral sclerosis or parkinsonism. Mean age at onset was 59.0 years old with a range of 44 to 70 years old, whilst average disease duration was 13.3 years with a range of 9.0 to 23.8 years. All had predominant left (more than right) temporal lobe atrophy on MRI.

(TABLE 1 about here)

In order to compare the pattern of neuroanatomical involvement in the presented case with the retrospective cohort of patients with TDP type C pathology we performed an analysis of their volumetric T1-weighted MRI scans (Figure 1), including the baseline scan of all cases with a disease duration of less than five years (in an attempt to capture the earliest features). In the final analysis we included 12 patients from the retrospective cohort as well as ten age-

matched healthy controls. A whole-brain parcellation using the geodesic information flow (GIF) algorithm (Cardoso et al, 2015), which is based on atlas propagation and label fusion, was performed. Labels were combined to create twenty cortical and four subcortical regions in each hemisphere as well as a brainstem region. Volumetric measures from the current nfvPPA patient as well as an average of the svPPA patients were expressed as a percentage of the mean control volume in each region (Figure 3).

(FIGURE 3 about here)

In the left frontal and insular regions, the volume of the brain in nfvPPA was lower than the svPPA group (e.g. left dorsolateral prefrontal cortex 78% of controls versus 96%), whereas temporal lobe (including hippocampal and amygdalar) volumes were lower in the svPPA group compared with the nfvPPA patient (Figure 3). This was more marked in the right temporal lobe: left amygdala – svPPA 61%, nfvPPA 66%; right amygdala – svPPA 79%, nfvPPA 93%; left hippocampus – svPPA 75%, nfvPPA 77%; right hippocampus – svPPA 86%, nfvPPA 95%.

Discussion

We present a case with clinical and imaging features of nfvPPA that was subsequently identified to have pathological findings typical of TDP-43 type C pathology, a variant usually found in association with svPPA.

The initial features of the clinical syndrome were consistent with the consensus criteria for nfvPPA with non-fluent, effortful speech; agrammatism; and relatively intact single-word

comprehension. Two other features, not within the criteria, are also more suggestive of nfvPPA than other variants. Binary reversals, such as the yes/no reversals exhibited here, often occur early in the disease course of PPA, and are thought to be more common in patients with nfvPPA than in other variants, with one study estimating a prevalence of at least 50% (Frattali et al., 2003; Warren et al., 2016). Abnormal laughter-like vocalisations, though less common than binary reversals, are another feature of PPA, and nfvPPA in particular. As in this case, they appear in lieu of verbal output, and tend to increase in frequency with disease progression; becoming most notable when patients are virtually mute. One study examining this phenomenon found that 6 of 10 PPA patients with abnormal laughter-like vocalisations had a diagnosis of nfvPPA (Rohrer et al., 2009).

Extrapyramidal signs (EPS) may be seen in PPA, and nfvPPA in particular. These may range from mild parkinsonism to a syndrome consistent with either progressive supranuclear palsy or corticobasal syndrome. Bradykinesia and rigidity are the most common EPS in FTD (Park et al., 2017) and can be useful in distinguishing nfvPPA from other variants. Bradykinesia was found to have a specificity of 0.98, and rigidity a specificity of 0.94, for nfvPPA in one case series (Kremen et al., 2011). Tremor is a rare feature of PPA, present in less than 6% of cases, and is usually resting or postural in nature (Kremen et al., 2011); when present, it may be part of a secondary diagnosis such as Parkinson's disease or essential tremor. In this case, the patient had received a prior diagnosis of essential tremor, but when seen in clinic two years after speech difficulty onset, increased tone and cogwheeling were demonstrable in her upper limbs, more suggestive of an extrapyramidal syndrome. EPS are strongly associated with tau pathology at post mortem (Spinelli et al., 2017) but can occur in those with TDP-43 pathology.

However, this is usually the type A form (e.g. in association with *GRN* mutations) and not type C pathology where there is usually no associated motor syndrome.

NfvPPA is an early-onset neurodegenerative disease, with an average age at onset of 63 years (Johnson et al., 2005). However, the range of age at onset is broad, and spans from the fourth decade to the ninth. Survival in nfvPPA ranges from two years (often in those with features of ALS) to twelve years, with an average duration of seven years (Grossman, 2012). This patient had a relatively old age of onset at 77, and a short disease duration of just three and a half years. This is particularly unusual in the context of patients with TDP-43 type C pathology as can be seen from the comparison with the UCL FTD retrospective cohort, with this patient above the top of the range of ages at onset, and below the bottom of the range of disease durations. It remains unclear what factors in this patient modified her clinical phenotype, but it is worth noting that this extends beyond the clinical features to also change the timing and rapidity of the neurodegenerative process.

Typical features of nfvPPA on MRI include atrophy of the left inferior frontal lobe, frontal operculum and anterior insula, which may extend further with disease progression to the superior anterior left temporal lobe, and the left prefrontal regions (Grossman, 2012). Involvement of the left frontal regions, operculum, and insula in the current case are in keeping with nfvPPA, but the presence of marked atrophy of the left temporal lobe (including medial structures) on a par with more typical TDP-43 type C cases (who present with svPPA) is unusual. Strikingly, whilst the pattern of antero-inferior and medial left temporal lobe involvement mirrored cases with svPPA, the right temporal lobe was relatively intact. This is likely to be an important factor in two major differences in the clinical presentation from

typical TDP-43 type C svPPA patients: the lack of behavioural change, with preservation of empathy in particular (Perry et al., 2001), and the presence of only mild semantic deficit early in the disease course. This second point is in keeping with studies that have demonstrated little or no semantic deficit with unilateral temporal lobe insults, as a result of resection, vascular event, or transcranial magnetic stimulation (Bi et al., 2011; Busigny et al., 2015; Lambon Ralph et al., 2010), and lends weight to the theory that both temporal lobes are crucial components of a bilateral and interconnected network representing semantic knowledge (Lambon Ralph et al., 2010; Pobric et al., 2010; Schapiro et al., 2013; Snowden et al., 2018), albeit with some degree of lateralisation of function between them (Woollams and Patterson, 2018). Indeed multiple longitudinal MRI studies have demonstrated that the majority of patients with svPPA have bilateral temporal lobe atrophy at baseline MRI (Brambati et al., 2009; Chan et al., 2001; Mummery et al., 2000; Rogalski et al., 2011; Rohrer et al., 2008), and in the rare instances where right temporal lobe atrophy is absent, semantic deficits are noted to be very mild (Mummery et al., 2000).

In summary, we describe an unusual case of TDP-43 type C pathology presenting with a predominantly nfvPPA clinical phenotype with atypical imaging features. As she progressed rapidly, assessment was limited and it may be that the severity of her non-fluent aphasia at this stage masked semantic deficits. However the history from her family was not suggestive of a semantic variant phenotype, and her presentation in clinic met the clinical diagnostic criteria for nfvPPA. Correlation of her unique radiological appearance and her clinical phenotype allows insight into normal brain function and lends support to the 'network' theory of semantic knowledge where both anterior temporal lobes are crucial to our ability to

hold semantic representations of the world. The case also highlights the importance of post mortem investigation of FTD spectrum disorders, where despite recent advances, there is still much to learn about the heterogeneity of the disease.

Acknowledgments

The authors acknowledge the support of the Medical Research Council UK, National Institute for Health Research (NIHR) Queen Square Dementia Biomedical Research Unit and the University College London Hospitals Biomedical Research Centre; the Leonard Wolfson Experimental Neurology Centre and the UK Dementia Research Institute. The Dementia Research Centre is an Alzheimer's Research UK coordinating centre and is supported by Alzheimer's Research UK, the Brain Research Trust and the Wolfson Foundation. JDW has received funding support from the Alzheimer's Society, Alzheimer's Research UK and by the NIHR UCLH Biomedical Research Centre. JDR is an MRC Clinician Scientist (MR/M008525/1) and has received funding from the NIHR Rare Diseases Translational Research Collaboration (BRC149/NS/MH), the Bluefield Project and the Association for Frontotemporal Degeneration. TL is funded by an Alzheimer's Research UK senior fellowship and the Leonard Wolfson Centre for Experimental Neurology. The Queen Square Brain Bank for Neurological disorders is supported by the Reta Lila Weston Institute for Neurological Studies and the Medical Research Council.

References

- Bi, Y., Wei, T., Wu, C., Han, Z., Jiang, T., and Caramazza, A. (2011). The role of the left anterior temporal lobe in language processing revisited: Evidence from an individual with ATL resection. Cortex *47*, 575–587.
- Bergeron D, Gorno-Tempini ML, Rabinovici GD, Santos-Santos MA, Seeley W, Miller BL, Pijnenburg Y, Keulen MA, Groot C, van Berckel BNM et al. (2018). Prevalence of amyloid-β pathology in distinct variants of primary progressive aphasia. Ann Neurol. *84(5):*729-740.
- Brambati, S.M., Rankin, K.P., Narvid, J., Seeley, W.W., Dean, D., Rosen, H.J., Miller, B.L., Ashburner, J., and Gorno-Tempini, M.L. (2009). Atrophy progression in semantic dementia with asymmetric temporal involvement: A tensor-based morphometry study. Neurobiology of Aging *30*, 103–111.
- Busigny, T., de Boissezon, X., Puel, M., Nespoulous, J.-L., and Barbeau, E.J. (2015). Proper name anomia with preserved lexical and semantic knowledge after left anterior temporal lesion: A two-way convergence defect. Cortex *65*, 1–18.
- Cardoso MJ, Modat M, Wolz R, Melbourne A, Cash D, Rueckert D, Ourselin S. Geodesic information flows: spatially-variant graphs and their application to segmentation and fusion. IEEE TMI 2015 doi: 10.1109/TMI.2015.2418298.
- Chan, D., Fox, N.C., Scahill, R.I., Crum, W.R., Whitwell, J.L., Leschziner, G., Rossor, A.M., Stevens, J.M., Cipolotti, L., and Rossor, M.N. (2001). Patterns of temporal lobe atrophy in semantic dementia and Alzheimer's disease. Annals of Neurology *49*, 433–442.
- Frattali, C., Duffy, J.R., Litvan, I., Patsalides, A.D., and Grafman, J. (2003). Yes/no reversals as neurobehavioral sequela: A disorder of language, praxis, or inhibitory control? Eur. J.

Neurol. *10*, 103–106.

- Gorno-Tempini ML, Hillis AE, Weintraub S, Kertesz A, Mendez M, Cappa SF, Ogar JM, Rohrer JD, Black S, Boeve BF et al. (2011). Classification of primary progressive aphasia and its variants. Neurology. *76(11):*1006-14.
- Grossman, M. (2010). Primary progressive aphasia: clinicopathological correlations. Nat. Rev. Neurol. *6*, 88–97.
- Grossman, M. (2012). The non-fluent/agrammatic variant of primary progressive aphasia. Lancet Neurol. *11*, 545–555.
- Johnson, J.K., Diehl, J., Mendez, M.F., Neuhaus, J., Shapira, J.S., Forman, M., Chute, D.J., Roberson, E.D., Pace-Savitsky, C., Neumann, M., et al. (2005). Frontotemporal lobar degeneration: demographic characteristics of 353 patients. Arch. Neurol. *62*, 925–930.
- Josephs KA, Hodges JR, Snowden JS, Mackenzie IR, Neumann M, Mann DM, Dickson DW (2011). Neuropathological background of phenotypical variability in frontotemporal dementia. Acta Neuropathol. *122(2):*137-53.
- Koriath C, Kenny J, Adamson G, Druyeh R, Taylor W, Beck J, Quinn L, Mok TH, Dimitriadis A, Norsworthy P, Bass N, Carter J, Walker Z, Kipps C, Coulthard E, Polke JM, Bernal-Quiros M, Denning N, Thomas R, Raybould R, Williams J, Mummery CJ, Wild EJ, Houlden H, Tabrizi SJ, Rossor MN, Hummerich H, Warren JD, Rowe JB, Rohrer JD, Schott JM, Fox NC, Collinge J, Mead S. (2018) Predictors for a dementia gene mutation based on gene-panel next-generation sequencing of a large dementia referral series. Mol Psychiatry. [Epub ahead of print].
- Kremen, S.A., Mendez, M.F., Tsai, P.-H., and Teng, E. (2011). Extrapyramidal Signs in the Primary Progressive Aphasias. Am. J. Alzheimers Dis. Dementias. *26*, 72–77.
- Lambon Ralph, M.A., Cipolotti, L., Manes, F., and Patterson, K. (2010). Taking both sides:

do unilateral anterior temporal lobe lesions disrupt semantic memory? Brain *133*, 3243–3255.

- Mackenzie IR, Neumann M, Baborie A, Sampathu DM, Du Plessis D, Jaros E, Perry RH, Trojanowski JQ, Mann DM, Lee VM (2011). A harmonized classification system for FTLD-TDP pathology. Acta Neuropathol. *122(1):*111-3.
- Mesulam, M.-M., Weintraub, S., Rogalski, E.J., Wieneke, C., Geula, C., and Bigio, E.H. (2014). Asymmetry and heterogeneity of Alzheimer's and frontotemporal pathology in primary progressive aphasia. Brain *137*, 1176–1192.
- Mummery, C.J., Patterson, K., Price, C.J., Ashburner, J., Frackowiak, R.S., and Hodges, J.R. (2000). A voxel-based morphometry study of semantic dementia: relationship between temporal lobe atrophy and semantic memory. Annals of Neurology *47*, 36–45.
- Neumann, M, Sampathu DM, Kwong LK, Truax AC, Micsenyi MC, Chou TT, Bruce J, Schuck T, Grossman M, Clark CM et al. (2006). Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. Science. *314(5796):*130-3.
- Park, H.K., Park, K.H., Yoon, B., Lee, J.-H., Choi, S.H., Joung, J.H., Yoon, S.J., Kim, B.C., Kim, S.H., Kim, E.-J., et al. (2017). Clinical characteristics of parkinsonism in frontotemporal dementia according to subtypes. J. Neurol. Sci. *372*, 51–56.
- Perry, R.J., Rosen, H.R., Kramer, J.H., Beer, J.S., Levenson, R.L., and Miller, B.L. (2001). Hemispheric dominance for emotions, empathy and social behaviour: evidence from right and left handers with frontotemporal dementia. Neurocase *7*, 145–160.
- Pobric, G., Jefferies, E., and Lambon Ralph, M.A. (2010). Amodal semantic representations depend on both anterior temporal lobes: Evidence from repetitive transcranial magnetic stimulation. Neuropsychologia *48*, 1336–1342.

- Rogalski, E., Cobia, D., Harrison, T.M., Wieneke, C., Weintraub, S., and Mesulam, M.-M. (2011). Progression of language decline and cortical atrophy in subtypes of primary progressive aphasia. Neurology *76*, 1804–1810.
- Rohrer, J.D., McNaught, E., Foster, J., Clegg, S.L., Barnes, J., Omar, R., Warrington, E.K., Rossor, M.N., Warren, J.D., and Fox, N.C. (2008). Tracking progression in frontotemporal lobar degeneration: serial MRI in semantic dementia. Neurology *71*, 1445–1451.
- Rohrer, J.D., Warren, J.D., and Rossor, M.N. (2009). Abnormal laughter-like vocalisations replacing speech in primary progressive aphasia. J. Neurol. Sci. *284*, 120–123.
- Rohrer, J.D., Lashley, T., Schott, J.M., Warren, J.E., Mead, S., Isaacs, A.M., Beck, J., Hardy, J., de Silva, R., Warrington, E., et al. (2011). Clinical and neuroanatomical signatures of tissue pathology in frontotemporal lobar degeneration. Brain *134*, 2565–2581.
- Schapiro, A.C., McClelland, J.L., Welbourne, S.R., Rogers, T.T., and Lambon Ralph, M.A. (2013). Why Bilateral Damage Is Worse than Unilateral Damage to the Brain. J. Cogn. Neurosci. *25*, 2107–2123.
- Snowden, J.S., Harris, J.M., Thompson, J.C., Kobylecki, C., Jones, M., Richardson, A.M., and Neary, D. (2018). Semantic dementia and the left and right temporal lobes. Cortex *107*, 188–203.
- Spinelli, E.G., Mandelli, M.L., Miller, Z.A., Santos-Santos, M.A., Wilson, S.M., Agosta, F., Grinberg, L.T., Huang, E.J., Trojanowski, J.Q., Meyer, M., et al. (2017). Typical and atypical pathology in primary progressive aphasia variants. Ann. Neurol. *81*, 430–443.
- Warren, J.D., Hardy, C.J., Fletcher, P.D., Marshall, C.R., Clark, C.N., Rohrer, J.D., and Rossor, M.N. (2016). Binary reversals in primary progressive aphasia. Cortex *82*, 287–289.
- Woollams, A.M., and Patterson, K. (2018). Cognitive consequences of the left-right asymmetry of atrophy in semantic dementia. Cortex *107*, 64–77.

TABLES and FIGURES

Table 1: Summary of cases with TDP-43 type C pathology within the UCL FTD cohort database

Case number	Diagnosis	Age at symptom onset	Age at death	Duration (years)	Amyotrophic lateral sclerosis?	Parkinsonism?
1	svPPA	59	73.0	14.0	0	0
2	svPPA	67	79.3	12.3	0	0
3	svPPA	55	73.7	18.7	0	0
4	svPPA	64	78.6	14.6	0	0
5	svPPA	64	74.3	10.3	0	0
6	svPPA	52	65.4	13.4	0	0
7	svPPA	44	67.8	23.8	0	0
8	svPPA	58	72.9	14.9	0	0
9	svPPA	67	76.0	9.0	0	0
10	svPPA	52	65.5	13.5	0	0
11	svPPA	70	83.8	13.8	0	0
12	svPPA	58	71.3	13.3	0	0
13	svPPA	54	68.4	14.4	0	0
14	svPPA	62	72.8	10.8	0	0
15	svPPA	50	65.2	15.2	0	0
16	svPPA	59	68.6	9.6	0	0
17	svPPA	67	75.7	8.7	0	0
18	svPPA	57	69.5	12.5	0	0
19	svPPA	50	66.7	16.7	0	0
20	svPPA	64	74.8	10.8	0	0
21	svPPA	69	80.3	11.3	0	0
22	svPPA	52	61.9	9.9	0	0
23	svPPA	50	64.4	14.4	0	0
24	svPPA	67	82.7	15.7	0	0
25	svPPA	64	75.5	11.5	0	0
	svPPA mean	**59.0**	**72.3**	**13.3**		
1	nfvPPA	77	80.3	3.3	0	1

Figure 1: Volumetric magnetic resonance images from the current case with nfvPPA (left column) and a representative case of svPPA from the retrospective TDP type C cohort (right column). Sagittal images at the top show the left hemisphere; coronal images in the middle and bottom show the left hemisphere on the right of the figure.

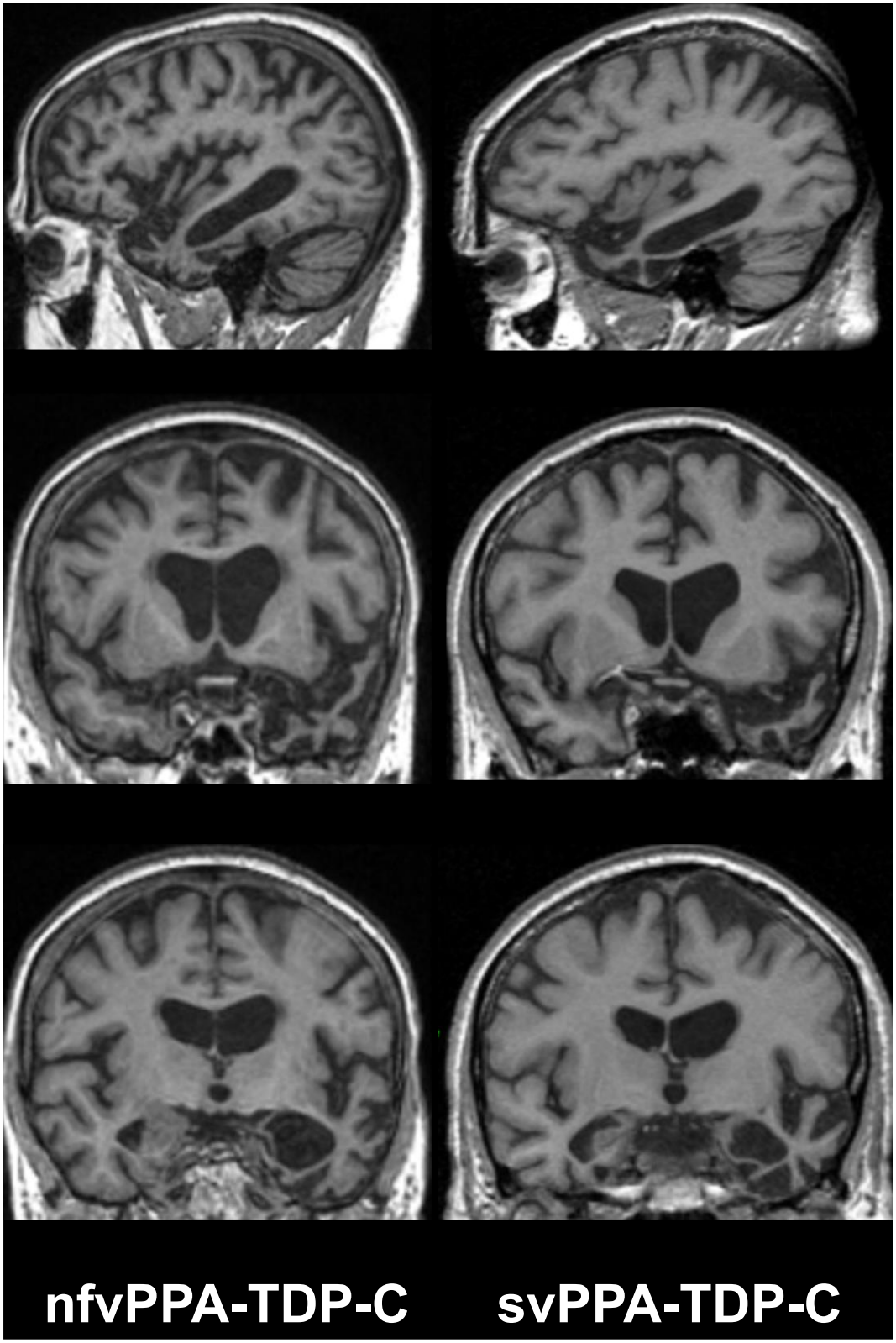

Figure 2: Macroscopic and microscopic findings in the nfvPPA patient: atrophy of the frontal (a, arrow) and temporal cortices (a, double arrow) was observed with enlargement of the lateral ventricle (a, asterisks). TDP-43 immunohistochemistry showed long twisted neurites in the grey matter of the frontal (b) and temporal cortices (c). Neuronal cytoplasmic inclusions were observed in the dentate fascia of the hippocampus (d, arrow). Classical FTLD-TDP type C pathology, long twisted neurites, were also observed in the anterior (e) and posterior (f) Broca's area. Bar in f represents 80μm in b and c; 30μm in d-f.

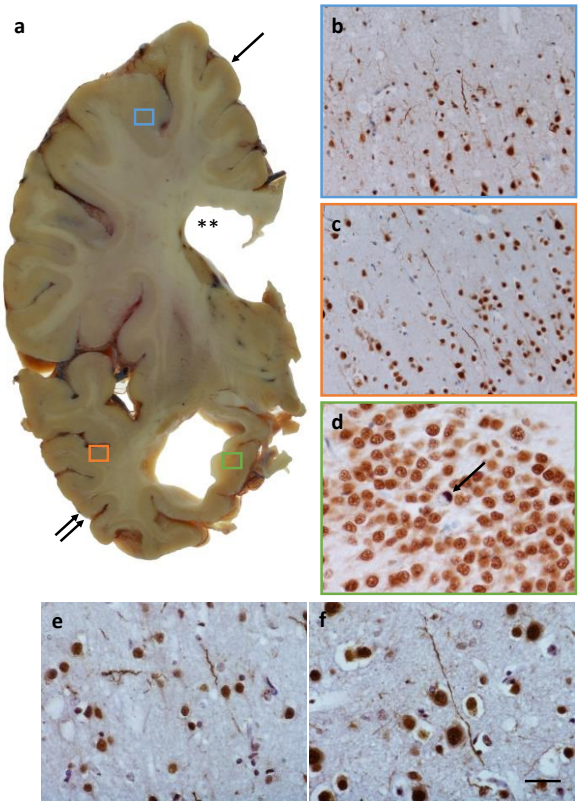

Figure 3: Diagram showing the relative regional volumes (expressed as a percentage of an age-matched healthy control cohort) in twenty cortical and four subcortical regions as well as a brainstem region. Dark blue represents the single case with nfvPPA and light blue represents the mean of the TDP-43 type C svPPA group. OFC = orbitofrontal cortex, DLPFC = dorsolateral prefrontal cortex, VMPFC = ventromedial prefrontal cortex, ant = anterior, post = posterior, lat = lateral, med = medial, supra temp = supratemporal, R = right, L = left).