Asymmetric pathology in primary progressive aphasia with progranulin mutations and TDP inclusions

Garam Kim, BA, BM*
Saman S. Ahmadian, MD*
Melanie Peterson, BS
Zach Parton, BA
Rohail Memon
Sandra Weintraub, PhD
Alfred Rademaker, PhD
Eileen Bigio, MD
M.-Marsel Mesulam, MD
Changiz Geula, PhD

Correspondence to Dr. Geula: c-geula@northwestern.edu

ABSTRACT

Objective: To investigate quantitative regional distribution and hemispheric asymmetry of TDP-43 (TAR DNA-binding protein 43) inclusions, neurons, and activated microglia in primary progressive aphasia (PPA) with progranulin (*GRN*) mutations, and to determine concordance between distribution of pathology, clinical phenotype, and known atrophy patterns.

Methods: Antibodies to phospho–TDP-43, NeuN (neuronal nuclei), and HLA-DR were used to visualize inclusions, neurons, and activated microglia in paraffin-embedded tissue sections from 4 participants with PPA: 2 of the agrammatic and 2 of the logopenic subtype. Unbiased stereological counting techniques were used for quantitation of immunoreactive profiles in language- and memory-related cortical areas bilaterally. Patterns of pathology across cortical areas and hemispheres were compared and their relationships with known patterns of atrophy investigated.

Results: Numerical densities of TDP-43 inclusions, and less so of activated microglia, were greater in language-related areas compared with memory-related areas. In language areas, neuronal density displayed a pattern opposite to inclusions and activated microglia. Densities of inclusions and microglia were greater ($p < 0.05$), and densities of neurons were lower ($p < 0.005$), in the left hemisphere compared with the right. In agrammatic PPA, the highest densities of TDP-43 inclusions were observed in left inferior or middle frontal gyri, and in logopenic participants, the highest density of inclusions was seen in left inferior parietal lobule. This distribution is consistent with subtype-specific peak atrophy sites.

Conclusions: Distribution of TDP-43 inclusions and neurons, and to a smaller extent of activated microglia, show a regional and hemispheric pattern consistent with disease phenotype and known patterns of atrophy in PPA with *GRN* mutations. ***Neurology*® 2016;86:627–636**

GLOSSARY

DN = dystrophic neurites; **FTLD** = frontotemporal lobar degeneration; ***GRN*** = progranulin; **HIP** = hippocampus/entorhinal cortex; **IFG** = inferior frontal gyrus; **IPL** = inferior parietal lobule; **MFG** = middle frontal gyrus; **NCI** = neuronal cytoplasmic inclusions; **NeuN** = neuronal nuclei; **NII** = neuronal intranuclear inclusions; **PPA** = primary progressive aphasia; **TDP-43** = TAR DNA-binding protein 43.

Primary progressive aphasia (PPA) is a neurodegenerative dementia characterized by dissolution of language as the principal clinical abnormality and relative preservation of other cognitive domains for most of the disease course.[1] Brains of patients with PPA display asymmetric atrophy of the perisylvian language network in the left hemisphere.[2,3] Approximately 60% of patients with PPA display pathologic inclusions characteristic of frontotemporal lobar degeneration (FTLD), including TAR DNA-binding protein 43 (TDP-43) inclusions (FTLD-TDP).[3]

Recent years have witnessed dazzling advances in the genetics of FTLD-TDP. Mutations in a number of genes, including the progranulin (*GRN*) gene,[4–7] valosin containing protein gene,[8,9] and *C9orf72* region on chromosome 9p (resulting in massive GGGGCC hexanucleotide repeat expansion in a noncoding region),[10,11] have been shown to cause FTLD-TDP, and *GRN* mutations are one cause of the pathologic subtype of PPA with TDP-43 inclusions (PPA-TDP). Despite breakthroughs in the genetics of TDP-43, quantitative information on the regional distribution of TDP-43 inclusions, and its relation to neuronal/glial abnormalities,

Supplemental data at Neurology.org

*These authors contributed equally to this work.

From the Cognitive Neurology and Alzheimer's Disease Center, Feinberg School of Medicine, Northwestern University, Chicago, IL.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

disease phenotype, and patterns of cortical atrophy, have not received extensive experimental attention.

In an earlier case study, we described the relationship between TDP-43 inclusions and disease phenotype in a patient with PPA carrying the *GRN* mutation.[12] Greater numbers of inclusions were observed in cortical areas affiliated with language function in the left hemisphere, when compared with the right, and when compared with the hippocampus, a memory-related area, in either hemisphere. This distribution pattern is consistent with progressive language deficits displayed by patients with PPA.[1,13] In the present study, we investigated the distribution of cortical TDP-43 inclusions and neurons in 4 participants with PPA carrying *GRN* mutations (including the previously reported case). Given the normal immunologic role of the progranulin (PGRN) protein, we also quantitatively analyzed the distribution of activated microglia in the same participants. Finally, we determined the relationship between quantitative measures of pathology and known patterns of atrophy based on reports in the literature.

METHODS

Participant information. Four Caucasian, right-handed participants were analyzed in this study. Further characteristics of the participants, including clinical course, are summarized in tables 1, e-1, and e-2 on the *Neurology*® Web site at Neurology.org.

The root diagnosis of PPA was rendered using an extensive battery of neuropsychological tests and criteria described previously.[1,3] Briefly, patients were required to have had insidious onset and gradual progression of a language impairment, manifested by deficits in word finding, word usage, word comprehension, or sentence construction. The aphasia should have initially arisen as the most salient impairment and as the principal factor underlying the disruption of activities of daily living.

Clinical PPA subtypes were identified based on published criteria.[14] Participants 1 and 2 displayed the agrammatic variant of PPA (tables 1 and e-1), characterized by disrupted sentence production, including abnormal word order, poor phrase structure, and misuse of grammatical morphemes. Participants 3 and 4 were classified as logopenic PPA, characterized by word retrieval deficits that lead to intermittent loss of verbal fluency.

Standard protocol approvals, registrations, and patient consents. Written informed consent for research was obtained from all participants or guardians. The Northwestern University institutional review board approved this study.

Tissue processing. Brains were fixed in formalin or paraformaldehyde. Blocks of tissue from regions of interest were embedded in paraffin, cut at a thickness of 5 μm, and mounted on slides. Sections were deparaffinized in xylenes and stained immunohistochemically using the avidin-biotin-peroxidase (ABC) method, utilizing the Vectastain Elite Kit, with streptavidin- or avidin-HRP, and diaminobenzidine or amino ethylcarbazole as chromogen.

Specific antibodies to TDP-43 phosphorylated at Ser409/410 (pS409/410-2; rabbit polyclonal; Cosmo Bio; 1/5,000), neuronal nuclear protein (NeuN, clone A60; mouse monoclonal; EMD Millipore; 1/1,000), and the major histocompatibility Class II cell surface receptor HLA-DR (mouse monoclonal; Dako; 1/800) were used to visualize inclusions, neurons, and activated microglia, respectively.

Unbiased stereological quantitation. Modified unbiased stereological quantitative methods were used to determine the density of TDP-43 inclusions, NeuN immunoreactive neurons, and activated microglia in cortical areas affiliated with language functions (inferior frontal gyrus [IFG]: Brodmann area 44; inferior parietal lobule [IPL]: area 39–40; and posterior aspects of superior temporal gyrus: area 22), or with memory (hippocampus/entorhinal cortex [HIP]), bilaterally. All cortical layers and hippocampal subregions were collectively assessed. In participants 1 and 2, counts from the middle frontal gyrus (MFG) (area 9), and in participant 4, counts from the inferior temporal gyrus (ITG) (area 20), were also analyzed. Densities of TDP-43 immunoreactive neuronal intranuclear inclusions (NII), neuronal cytoplasmic inclusions (NCI), and dystrophic neurites (DN) were determined separately.

For each stain, 5 adjacent sections per area were used for stereological analysis using the optical fractionator method and the Stereo Investigator software (MBF Bioscience, MicroBrightField, Williston, VT), by an observer blinded to participant, cortical area, and hemisphere as previously described.[15] The top and bottom 1 μm of each section was designated as guard height. The boundaries of each cortical area were delineated at 1× magnification and counting was performed at

Table 1 Characteristics of participants

Study participant	Age, y	Sex	Education, y	Disease duration, y	PPA clinical subtype	Postmortem interval, h	Mode of fixation	*GRN* mutation
1	61	F	12	5	Agrammatic	17	4% PFA	c.675_676delCA (p.Pro225ProfsX28)
2	56	F	18	6	Agrammatic	11	Formalin	c.910_911insTG (p.Trp304LeufsX58)
3	61	M	24	8	Logopenic	12	Formalin	c.5913A>G (IVS6-2A>G)
4	67	F	NA	6	Logopenic	24	Formalin	c.1477C>T, exon 11, in one allele

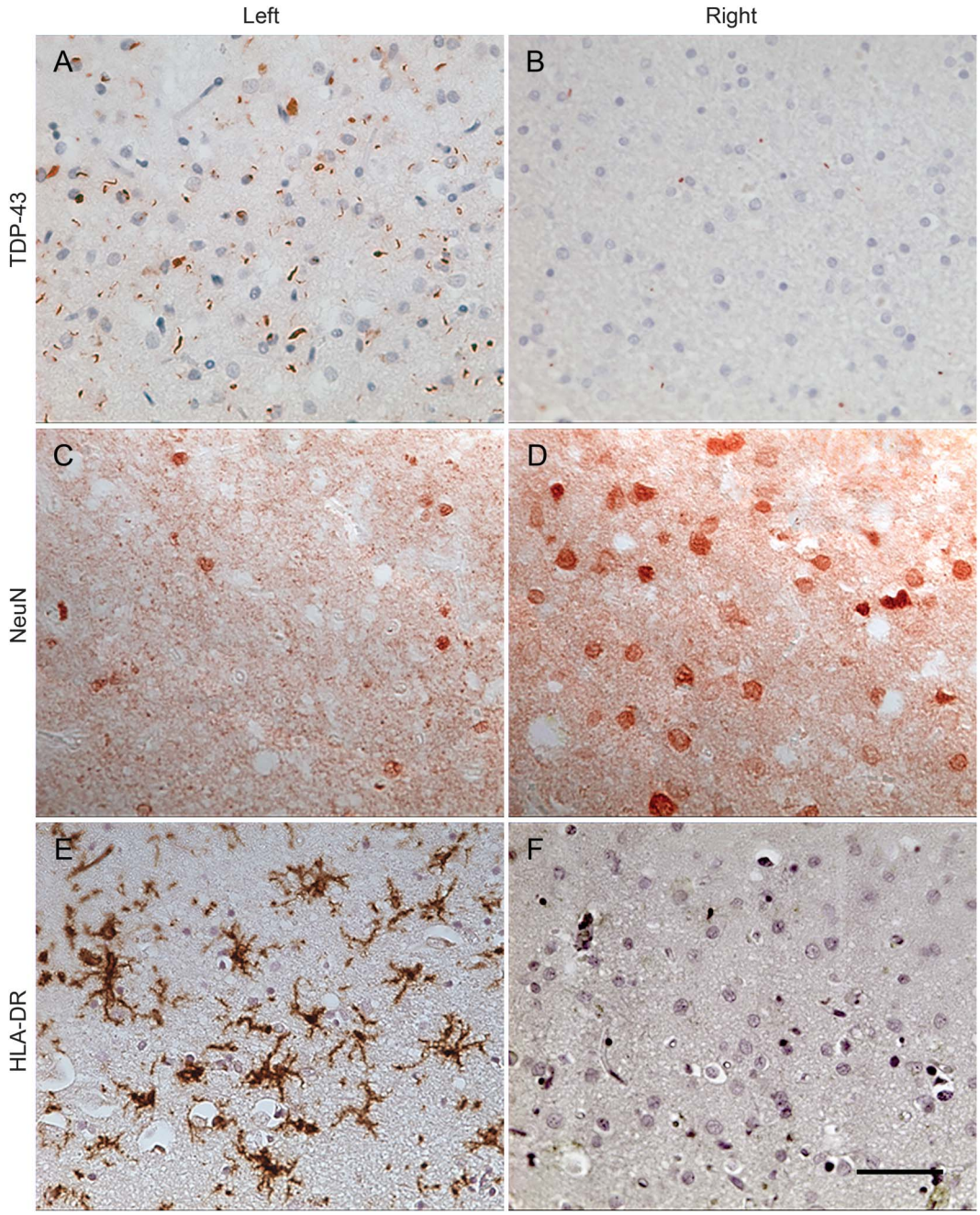
Abbreviations: NA = not available; PFA = paraformaldehyde; PPA = primary progressive aphasia.

60×. The specific parameters used in this investigation were derived from pilot studies on a subsample of participants to determine optimal settings that would result in coefficient of error less than 0.1.

Statistical analysis. Density of TDP-43 inclusions, NeuN immunoreactive neurons, and activated microglia were compared across areas and hemispheres using mixed linear models taking into account repeated measures within samples and nonnormality of the data. Post hoc comparisons were done using pairwise *t* tests. Spearman correlation analyses were used to determine relationships between measures.

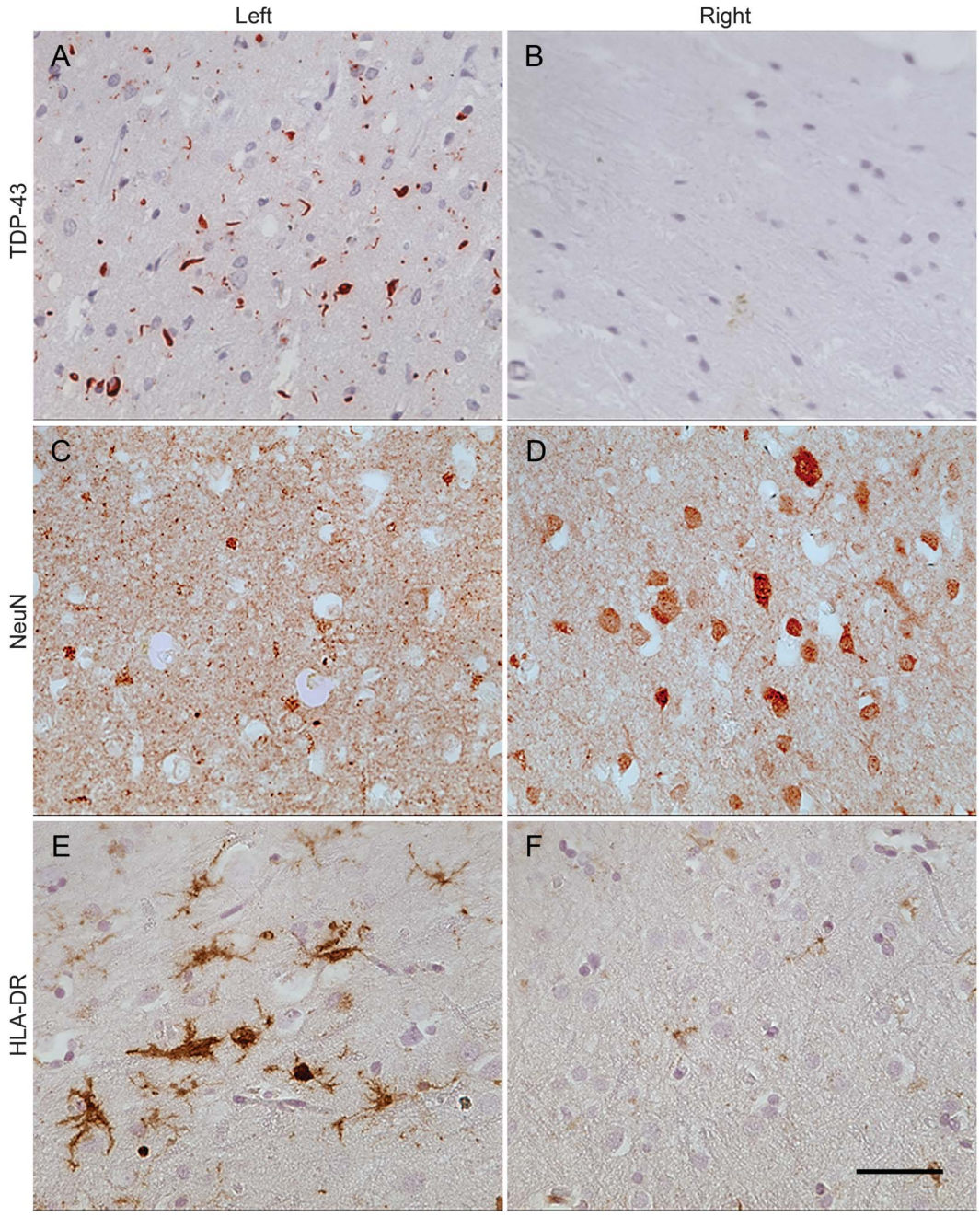
RESULTS All cortical areas examined contained TDP-43 inclusions, NeuN immunoreactive neurons, and activated microglia (figures 1–4). While TDP-43–positive NII, NCI, and short/thin DN were present in each brain, the overall density of DN was considerably higher than the other

Figure 1 Asymmetric distribution of pathology in a participant with agrammatic primary progressive aphasia



Substantially greater numbers of TDP-43 inclusions (A and B) and activated microglia (E and F), and considerably fewer NeuN immunoreactive neurons (C and D) were present in the middle frontal gyrus within the left hemisphere of participant 1 (A, C, and E) when compared with the right (B, D, and F). Note higher density of TDP-43 immunoreactive dystrophic neurites when compared with neuronal intranuclear inclusions and neuronal cytoplasmic inclusions in panel A. Scale bar in F is 50 μm and also applies to A–E. NeuN = neuronal nuclei; TDP-43 = TAR DNA-binding protein 43.

Figure 2 Asymmetric distribution of pathology in a participant with logopenic primary progressive aphasia

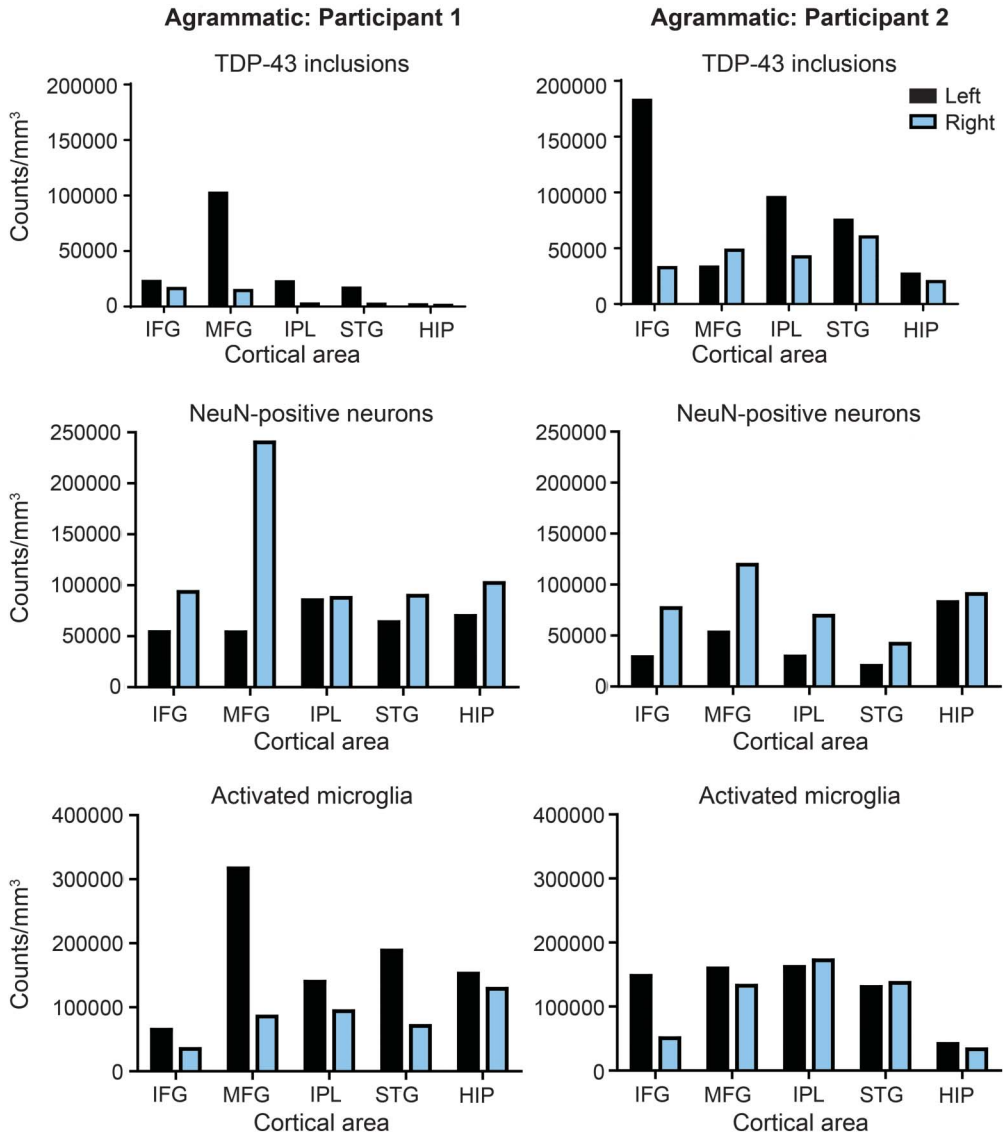


Substantially greater numbers of TDP-43 inclusions (A and B, participant 3) and activated microglia (E and F, participant 4), and considerably fewer NeuN immunoreactive neurons (C and D, participant 4) were present in the inferior parietal lobule within the left hemisphere (A, C, and E) when compared with the right (B, D, and F). Note higher density of TDP-43 immunoreactive dystrophic neurites when compared with neuronal intranuclear inclusions and neuronal cytoplasmic inclusions in panel A. Scale bar in F is 50 μm and also applies to A–E. NeuN = neuronal nuclei; TDP-43 = TAR DNA-binding protein 43.

inclusions (figures 1A and 2A). In the 4 participants, the density of cortical DN was 11- to 35-fold higher than the density of NII ($p < 0.05$) and 2- to 5-fold higher than the density of NCI. The density of NCI was 3- to 6-fold higher than the density of NII. This pattern of inclusion density is consistent with FTLD-TDP type A.[16,17] NeuN immunoreactivity was observed in neuronal nuclei and cytoplasm (figures 1C and 2C) while HLA-DR immunoreactivity was present in enlarged microglia and their processes (figures 1E and 2E).

The numerical density of immunoreactive elements displayed considerable variation among cortical areas, and this variation was not uniform across participants. In participants 1 and 2, classified as the agrammatic subtype of PPA, the highest densities of TDP-43 inclusions were encountered in the language regions of the frontal cortex (IFG or MFG, figure 3), while in

Figure 3 Density of cortical pathology in participants with agrammatic PPA

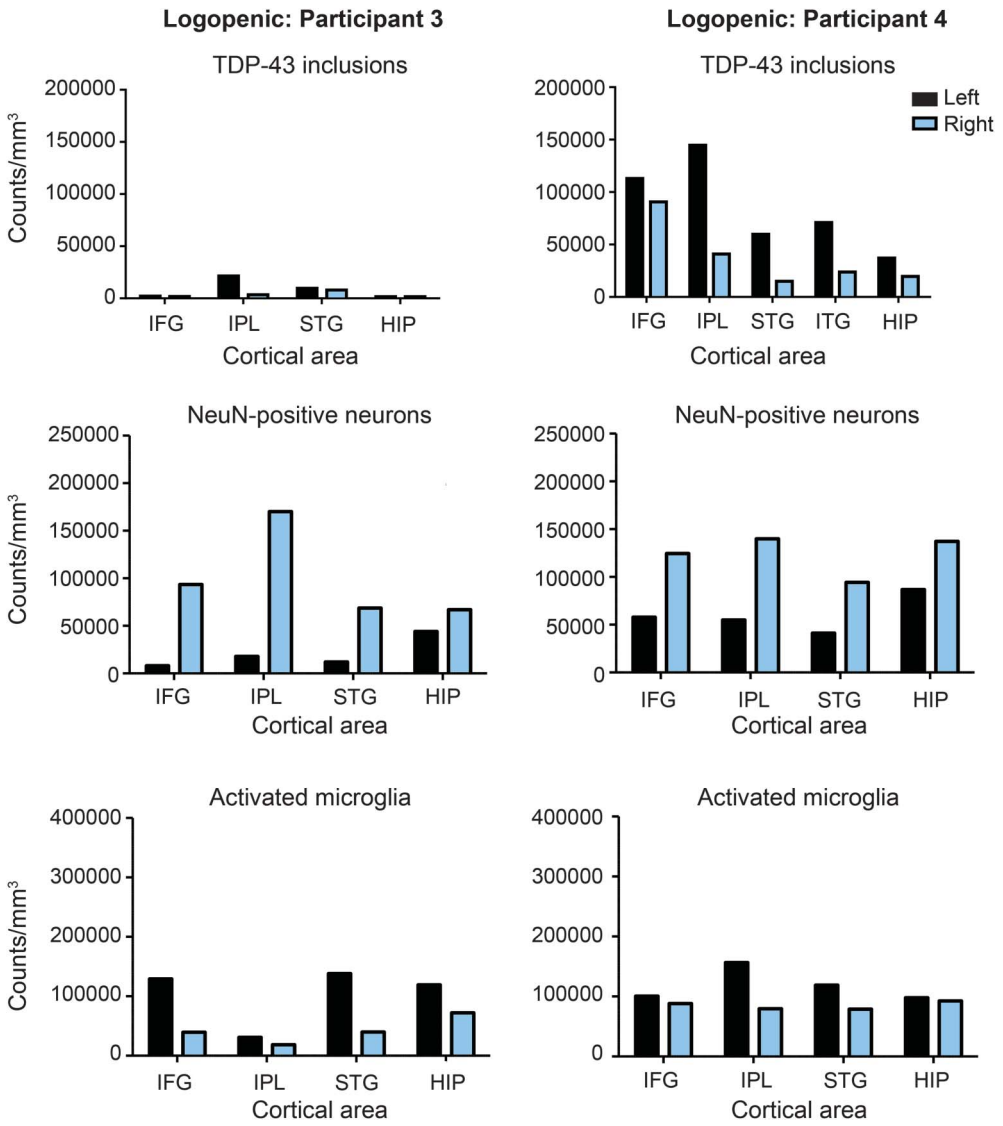


Density of TDP-43 inclusions, NeuN immunoreactive neurons, and activated microglia within the cortical areas examined in the 2 participants with agrammatic PPA. Note the general asymmetry of pathology favoring the left hemisphere, the peak density of inclusions and relatively low density of neurons in the language areas of MFG or IFG in the left hemisphere, and the lowest densities of inclusions in the HIP, a memory-related region. HIP = entorhinal cortex/hippocampus; IFG = inferior frontal gyrus; IPL = inferior parietal lobule; MFG = middle frontal gyrus; NeuN = neuronal nuclei; PPA = primary progressive aphasia; STG = superior temporal gyrus; TDP-43 = TAR DNA-binding protein 43.

participants 3 and 4, categorized as logopenic PPA, the highest densities of inclusions were seen in the parietal language area (IPL, figure 4). Other regions displayed lower densities of inclusions and the HIP consistently displayed among the lowest densities. The regional densities of NeuN immunoreactive neurons in language areas generally displayed a pattern opposite to TDP-43 inclusions. Activated microglia exhibited the least variation across participants and cortical areas primarily due to high densities in many regions (figures 3 and 4). Nevertheless, in 2 of the 4 participants (participants 1 and 4), cortical areas with the highest densities of inclusions also had the highest densities of activated microglia. Furthermore, higher densities of activated microglia showed significant correspondence to higher densities of TDP-43 inclusions ($r = 0.43$, $p < 0.01$) and lower densities of NeuN immunoreactive neurons ($r = -0.34$, $p < 0.05$).

Hemispheric asymmetry of pathology. With few exceptions, cortical areas in the left hemisphere displayed higher densities of TDP-43 inclusions and activated microglia, and lower densities of NeuN immunoreactive neurons (figures 1–4). In instances in which the densities did not follow the pattern described, the 2 hemispheres displayed nearly equal

Figure 4 Density of cortical pathology in participants with logopenic PPA



Density of TDP-43 inclusions, NeuN immunoreactive neurons, and activated microglia within the cortical areas examined in the 2 participants with logopenic PPA. Note the general asymmetry of pathology favoring the left hemisphere, the peak density of inclusions and relatively low density of neurons in the language area IPL in the left hemisphere, and the lowest densities of inclusions in the HIP, a memory-related region. HIP = entorhinal cortex/hippocampus; IFG = inferior frontal gyrus; IPL = inferior parietal lobule; ITG = inferior temporal gyrus; MFG = middle frontal gyrus; STG = superior temporal gyrus.

densities. The opposite pattern was not encountered. Overall, the higher densities of the 3 types of TDP-43 inclusions combined and of DN approached statistical significance in the left hemisphere when compared with the right ($p < 0.06$ and $p < 0.065$, respectively). Significantly higher densities of NeuN immunoreactive neurons were encountered in the right hemisphere when compared with the left ($p < 0.005$), and significantly higher densities of activated microglia were observed in the left hemisphere when compared with the right ($p < 0.05$).

Relationship of pathology to known patterns of atrophy. Cortical atrophy in PPA varies based on predominant clinical symptoms and subtype (agrammatic, logopenic, or semantic). Specifically, structural MRI studies indicate that at first visit, patients who have the agrammatic subtype of PPA display peak atrophy in IFG and MFG, as well as in superior and middle temporal gyri, and patients who have the logopenic subtype display peak atrophy in the IPL, and posterior aspects of all temporal gyri, within the left hemisphere.[2,13,18] Atrophy spreads to encompass the entire perisylvian language network at 2-year follow-up. However, the hemispheric asymmetry remains, the above regions continue to display substantial atrophy, and significant atrophy is confined to the language network.

While quantitative structural MRI data were not available from the 4 participants reported in this study, the distribution pattern of peak pathology

was generally concordant with the initial pattern of atrophy summarized above. Peak density of TDP-43 inclusions was observed in one of the areas known to display atrophy in each subtype. Thus, in the 2 participants classified as agrammatic subtype of PPA (participants 1 and 2), the highest densities of TDP-43 inclusions were observed in IFG or MFG, and in the 2 logopenic participants, the highest density of inclusions were seen in IPL (figures 3 and 4).

Hemispheric asymmetry of pathology was also most pronounced in the regions discussed above. When data from areas of peak expected atrophy with the highest densities of TDP-43 inclusions in the left hemisphere were pooled in the 4 participants (IFG and MFG in agrammatic participants and IPL in logopenic participants), significantly greater density of TDP-43 inclusions was observed in these left hemisphere areas when compared with all cortical regions on the right ($p < 0.009$), and the difference approached significance when such areas on the left were compared with the remainder of cortical areas on the left ($p < 0.06$). Conversely, density of NeuN immunoreactive neurons in these areas on the left was significantly smaller than all other areas on the right ($p < 0.001$) and was generally at the same level when compared with the remainder of areas on the left ($p > 0.05$). Similar comparisons of activated microglia density did not reach statistical significance ($p > 0.05$).

DISCUSSION Aggregation and propagation of misfolded proteins in the form of abnormal inclusions is a common feature of neurodegenerative diseases. The exact relationships of the resultant inclusions to neuronal loss and cortical atrophy are incompletely understood. In some settings, such as Huntington disease, the Huntingtin inclusions may reflect neuroprotective processes.[19] In other neurodegenerative disorders, such as Alzheimer disease, the phosphorylated tau precipitates in the neurofibrillary tangles are thought to trigger neuronal death so that neurofibrillary tangle densities become tightly correlated with regional atrophy and dysfunction.[20,21]

In the present study of a relatively small sample of participants, greater densities of inclusions in specific cortical areas in PPA-TDP with *GRN* mutations corresponded to lower densities of NeuN immunoreactive neurons, and to a smaller extent, higher densities of activated microglia. Substantially greater densities of inclusions and activated microglia, and lower densities of neurons, were encountered in cortical areas in the left hemisphere compared with areas on the right. Within the left hemisphere, the numerical densities of inclusions and to a smaller extent activated microglia were greater in cortical areas affiliated with language function than areas associated with memory. In the agrammatic subtype (participants 1 and 2), the highest densities of TDP-43 inclusions were observed in IFG or MFG, and in the logopenic participants, the highest density of inclusions was seen in the left IPL. This distribution is consistent with subtype-specific peak atrophy sites. Therefore, the distribution of pathology in these participants displays concordance with the clinical PPA phenotype, characterized by predominant abnormalities in language function mediated by the language-dominant left hemisphere in right-handed individuals.[1]

There were notable variations among participants, particularly in the overall density of TDP-43 inclusions. Thus, participant 1 (agrammatic PPA) and participant 3 (logopenic PPA) displayed substantially lower densities of TDP-43 inclusions than did participants 2 or 4. At present, the relationship between variations in the overall density of TDP-43 inclusions and clinical presentation is unknown. There were no clear differences in clinical presentation among the participants other than the PPA subtype. However, it is noteworthy that participant 4, a logopenic PPA with higher density of TDP-43 inclusions, displayed abnormalities in several neuropsychological tests (table e-2) not observed in the second logopenic participant. In participants 1 and 2 with agrammatic PPA, the highest density and asymmetry of TDP-43 inclusions were observed in MFG and IFG, respectively, both of which display peak atrophy in this PPA subtype. This distribution pattern suggests that pathology in cortical areas that partially disconnect language regions (in this case disrupting access of IFG to a normal functioning MFG) is sufficient to produce a language deficit. Finally, consistent with the spread of pathology to other language regions as disease progresses, IPL showed the second highest density and asymmetry of TDP-43 inclusions in agrammatic participant 2.

In this study, TDP-43 pathology and *GRN* mutations were associated with 2 different PPA clinical subtypes. This finding is consistent with our recent observations in 6 participants with PPA who had type-A TDP pathology.[3] Four of the 6 participants in that study presented clinically as logopenic PPA, while the remaining 2 were of the agrammatic subtypes, and one participant per subtype had a *GRN* mutation. Another study of 6 participants with agrammatic PPA[22] reported that all had the postmortem diagnosis of FTLD-TDP, and 4 had *GRN* mutations. Thus, while TDP pathology with *GRN* mutations can result in the agrammatic subtype of PPA, it can alternatively result in logopenic PPA.

Among other functions, the PGRN protein is involved in immunity and acts in an anti-inflammatory manner.[23] PGRN is present in microglia,[24] acts as a chemoattractant for microglia recruitment,[25] stimulates microglia endocytic activity,[25] and is increased in neuroinflammatory conditions.[24] It binds to tumor necrosis factor receptors, interferes with the interaction of the potentially cytotoxic tumor necrosis factor α with its receptors and is thereby therapeutic against inflammatory arthritis in mice.[26] Haploinsufficiency caused by *GRN* mutations in FTLD-TDP results in significantly elevated serum levels of the proinflammatory cytokine interleukin 6 compared with patients without the *GRN* mutation.[27] Finally, PGRN deficiency promotes neuroinflammation through microglia activation, resulting in enhanced neuronal loss in experimentally induced damage,[28] and causes exaggerated inflammation in mice.[29] Thus, microglia activation and inflammation are likely involved in the neurodegenerative process in FTLD- and PPA-TDP, at least in those with *GRN* mutations.

In the present study of participants with PPA and *GRN* mutations, densities of activated microglia did not show the same pronounced differences among cortical areas as did the densities of inclusions and neurons, and they did not reliably identify cortical regions of greatest atrophy. One potential factor contributing to these results may be overall increased activation of microglia throughout the cerebral cortex mediated by reduced PGRN protein. Thus, regardless of the extent of other pathology, microglia would show exacerbated activation across all cortical areas affected. It is equally possible that microglia show a pronounced and early response to TDP-43 pathology and neuronal loss and are maximally activated regardless of the degree of pathology or *GRN* mutation. Testing these possibilities must await investigation of microglia activation in participants with PPA but without *GRN* mutations. In the present study, the density of microglia did show significant correlations with the densities of inclusions and neurons, reinforcing the possibility that microglia may make a significant contribution to cortical abnormalities in PPA and FTLD with *GRN* mutations. Despite the lowest densities of TDP-43 inclusions, the hippocampus contained substantial densities of microglia. It remains to be determined whether this disproportionate distribution of microglia is related to *GRN* mutations.

Cortical neuronal loss is an established feature of FTLD.[16,30] However, quantitative regional variations in loss of neurons has not received experimental attention in FTLD-TDP. Investigations in transgenic animal models have demonstrated a relationship between human TDP-43 overexpression and loss of cortical neurons.[31–33] Nearly all assessments of neuronal loss in FTLD-TDP, including PPA-TDP, have used qualitative rankings. An investigation of TDP-43 inclusions using nonstereological quantitative techniques showed no significant differences in the density of remaining neurons in the MFG, ITG, and HIP.[34] The only unbiased stereological investigation of regional loss of cortical neurons in FTLD-TDP found significant loss of neurons in the parolfactory cortex when compared to controls.[35]

The present study utilized unbiased stereological analysis of the status of cortical neurons in PPA-TDP. Significantly lower densities of neurons were encountered in cortical areas of the left hemisphere, and this asymmetry attained its peak in at least one cortical area known to undergo peak atrophy in each PPA subtype. However, it should be noted that the measures obtained in the present study are not based on comparisons with the normal contingent of neurons in each brain area. Therefore, definitive conclusions must await investigations that include an age-matched control group. Nonetheless, our results point to likely regional and hemispheric differences in the extent of neuronal loss in PPA that display concordance with disease phenotype and PPA subtype.

Extracellular inclusions have not been reported in FTLD-TDP. Therefore, it is assumed that inclusions disappear as neurons are lost. Our findings of increased numbers of inclusions in areas of neuronal loss would suggest that areas with greatest neuronal loss have higher propensity for inclusion formation and new inclusions are generated as old ones disappear with dying neurons. Based on accepted pathologic criteria, FTLD-TDP type A is associated with infrequent NCI and NII and predominance of short, thin DN. It is possible that in FTLD-TDP type A, the lower numbers of NCI and NII are caused by loss of neurons.

The results of the present study demonstrate regional and hemispheric distribution of pathology in PPA-TDP that is concordant with disease phenotype and subtype-specific patterns of atrophy. We have demonstrated similar asymmetric distribution of plaques and tangles in PPA participants with Alzheimer disease pathology.[15] Therefore, it appears that the PPA phenotype is determined by the anatomical distribution of neurodegeneration rather than the cellular and molecular nature of the pathology.

AUTHOR CONTRIBUTIONS

G. Kim contributed to the design and conceptualization of the study, analysis and interpretation of data, and drafting the manuscript. S.S. Ahmadian contributed to the design and conceptualization of the study, analysis and interpretation of data, and revising the manuscript for intellectual content. M. Peterson contributed to the design of the study and analysis of data. Z. Parton contributed to the design of the study and

analysis of data. R. Memon contributed to the design of the study and analysis of data. S. Weintraub contributed to revising the manuscript for intellectual content. A. Rademaker contributed to analysis of data. E. Bigio contributed to design of the study and revising the manuscript for intellectual content. M.-M. Mesulam contributed to the design and conceptualization of the study and revising the manuscript for intellectual content. C. Geula contributed to the design and conceptualization of the study, analysis and interpretation of data, and drafting and revising the manuscript for intellectual content.

STUDY FUNDING

This work was supported by grants from the National Institute of Neurological Disorders and Stroke (NS085770), The Louis Family Foundation, and National Institute on Aging Northwestern University Alzheimer's Disease Center (AG013854).

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

Received June 12, 2015. Accepted in final form October 22, 2015.

REFERENCES

1. Mesulam MM, Rogalski EJ, Wieneke C, et al. Primary progressive aphasia and the evolving neurology of the language network. Nat Rev Neurol 2014;10:554–569.
2. Rogalski E, Cobia D, Martersteck A, et al. Asymmetry of cortical decline in subtypes of primary progressive aphasia. Neurology 2014;83:1184–1191.
3. Mesulam MM, Weintraub S, Rogalski EJ, Wieneke C, Geula C, Bigio EH. Asymmetry and heterogeneity of Alzheimer's and frontotemporal pathology in primary progressive aphasia. Brain 2014;137:1176–1192.
4. Baker M, Mackenzie IR, Pickering-Brown SM, et al. Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17. Nature 2006;442:916–919.
5. Yu CE, Bird TD, Bekris LM, et al. The spectrum of mutations in progranulin: a collaborative study screening 545 cases of neurodegeneration. Arch Neurol 2010;67:161–170.
6. Chen-Plotkin AS, Martinez-Lage M, Sleiman PM, et al. Genetic and clinical features of progranulin-associated frontotemporal lobar degeneration. Arch Neurol 2011;68:488–497.
7. Beck J, Rohrer JD, Campbell T, et al. A distinct clinical, neuropsychological and radiological phenotype is associated with progranulin gene mutations in a large UK series. Brain 2008;131:706–720.
8. Spina S, Van Laar AD, Murrell JR, et al. Phenotypic variability in three families with valosin-containing protein mutation. Eur J Neurol 2013;20:251–258.
9. Nalbandian A, Donkervoort S, Dec E, et al. The multiple faces of valosin-containing protein-associated diseases: inclusion body myopathy with Paget's disease of bone, frontotemporal dementia, and amyotrophic lateral sclerosis. J Mol Neurosci 2011;45:522–531.
10. Hsiung GY, DeJesus-Hernandez M, Feldman HH, et al. Clinical and pathological features of familial frontotemporal dementia caused by C9ORF72 mutation on chromosome 9p. Brain 2012;135:709–722.
11. DeJesus-Hernandez M, Mackenzie IR, Boeve BF, et al. Expanded GGGGCC hexanucleotide repeat in noncoding region of C9ORF72 causes chromosome 9p-linked FTD and ALS. Neuron 2011;72:245–256.
12. Gliebus G, Bigio EH, Gasho K, et al. Asymmetric TDP-43 distribution in primary progressive aphasia with progranulin mutation. Neurology 2010;74:1607–1610.
13. Mesulam MM, Wieneke C, Thompson C, Rogalski E, Weintraub S. Quantitative classification of primary progressive aphasia at early and mild impairment stages. Brain 2012;135:1537–1553.
14. Gorno-Tempini ML, Hillis AE, Weintraub S, et al. Classification of primary progressive aphasia and its variants. Neurology 2011;76:1006–1014.
15. Gefen T, Gasho K, Rademaker A, et al. Clinically concordant variations of Alzheimer pathology in aphasic versus amnestic dementia. Brain 2012;135:1554–1565.
16. Mackenzie IR, Baborie A, Pickering-Brown S, et al. Heterogeneity of ubiquitin pathology in frontotemporal lobar degeneration: classification and relation to clinical phenotype. Acta Neuropathol 2006;112:539–549.
17. Mackenzie IR, Neumann M, Baborie A, et al. A harmonized classification system for FTLD-TDP pathology. Acta Neuropathol 2011;122:111–113.
18. Rogalski E, Cobia D, Harrison TM, et al. Anatomy of language impairments in primary progressive aphasia. J Neurosci 2011;31:3344–3350.
19. Arrasate M, Mitra S, Schweitzer ES, Segal MR, Finkbeiner S. Inclusion body formation reduces levels of mutant huntingtin and the risk of neuronal death. Nature 2004;431:805–810.
20. Arnold SE, Hyman BT, Flory J, Damasio AR, Van Hoesen GW. The topographical and neuroanatomical distribution of neurofibrillary tangles and neuritic plaques in the cerebral cortex of patients with Alzheimer's disease. Cereb Cortex 1991;1:103–116.
21. Arriagada PV, Growdon JH, Hedley-Whyte ET, Hyman BT. Neurofibrillary tangles but not senile plaques parallel duration and severity of Alzheimer's disease. Neurology 1992;42:631–639.
22. Deramecourt V, Lebert F, Debachy B, et al. Prediction of pathology in primary progressive language and speech disorders. Neurology 2010;74:42–49.
23. Jian J, Konopka J, Liu C. Insights into the role of progranulin in immunity, infection, and inflammation. J Leukoc Biol 2013;93:199–208.
24. Ahmed Z, Mackenzie IR, Hutton ML, Dickson DW. Progranulin in frontotemporal lobar degeneration and neuroinflammation. J Neuroinflammation 2007;4:7.
25. Pickford F, Marcus J, Camargo LM, et al. Progranulin is a chemoattractant for microglia and stimulates their endocytic activity. Am J Pathol 2011;178:284–295.
26. Tang W, Lu Y, Tian QY, et al. The growth factor progranulin binds to TNF receptors and is therapeutic against inflammatory arthritis in mice. Science 2011;332:478–484.
27. Bossu P, Salani F, Alberici A, et al. Loss of function mutations in the progranulin gene are related to pro-inflammatory cytokine dysregulation in frontotemporal lobar degeneration patients. J Neuroinflammation 2011;8:65.
28. Martens LH, Zhang J, Barmada SJ, et al. Progranulin deficiency promotes neuroinflammation and neuron loss following toxin-induced injury. J Clin Invest 2012;122:3955–3959.
29. Yin F, Banerjee R, Thomas B, et al. Exaggerated inflammation, impaired host defense, and neuropathology in

progranulin-deficient mice. J Exp Med 2010;207:117–128.
30. Sampathu DM, Neumann M, Kwong LK, et al. Pathological heterogeneity of frontotemporal lobar degeneration with ubiquitin-positive inclusions delineated by ubiquitin immunohistochemistry and novel monoclonal antibodies. Am J Pathol 2006;169:1343–1352.
31. Cannon A, Yang B, Knight J, et al. Neuronal sensitivity to TDP-43 overexpression is dependent on timing of induction. Acta Neuropathol 2012;123:807–823.
32. Xu YF, Gendron TF, Zhang YJ, et al. Wild-type human TDP-43 expression causes TDP-43 phosphorylation, mitochondrial aggregation, motor deficits, and early mortality in transgenic mice. J Neurosci 2010;30:10851–10859.
33. Xu YF, Zhang YJ, Lin WL, et al. Expression of mutant TDP-43 induces neuronal dysfunction in transgenic mice. Mol Neurodegener 2011;6:73.
34. Armstrong RA, Carter D, Cairns NJ. A quantitative study of the neuropathology of 32 sporadic and familial cases of frontotemporal lobar degeneration with TDP-43 proteinopathy (FTLD-TDP). Neuropathol Appl Neurobiol 2012;38:25–38.
35. Cairns NJ, Brannstrom T, Khan MN, Rossor MN, Lantos PL. Neuronal loss in familial frontotemporal dementia with ubiquitin-positive, tau-negative inclusions. Exp Neurol 2003;181:319–326.