Published in final edited form as:

Neuropathol Appl Neurobiol. 2014 October ; 40(6): 778–782. doi:10.1111/nan.12144.

Adult Polyglucosan Body Disease with *GBE1* Haploinsufficiency and Concomitant Frontotemporal Lobar Degeneration

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Keywords

adult polyglucosan body disease; *GBE1*; haploinsufficiency; FTL-D-FUS; aFTLD-U; FTL-D-TDP

Recently, Farmer et al. described the case of a 54-year-old Ashkenazi Jewish woman with a five-year course of progressive **behavioral variant frontotemporal dementia (bvFTD)** who was found at autopsy to have both **adult polyglucosan body disease (APBD)** (not, however, proven genetically) and frontotemporal lobar degeneration with TDP-43 proteinopathy (FTLD-TDP) [1]. We present the clinical, pathologic, molecular, and genetic findings in a novel case of APBD with *GBE1* haploinsufficiency and concomitant frontotemporal lobar degeneration with FUS proteinopathy (FTLD-FUS), as well as the second reported case of APBD with concomitant FTL-D-TDP. We also investigated 52 additional FTL-D cases for the presence of concomitant APBD.

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Authors' Contributions: Esther N Bit-Ivan, Kyung-Hwa Lee, Darren Gitelman, and Eileen H Bigio were responsible for the pathologic analysis of the APBD + FTL-D-FUS patient and drafting and revising the manuscript. Eileen H Bigio analyzed the additional FTL-D-TDP and FTL-D-FUS cases for concomitant APBD. Sandra Weintraub, Darren Gitelman, and Marsel Mesulam were responsible for the clinical evaluation of the proband. Rosa Rademakers, Adrian M. Isaacs, Orhan Akma, and Salvatore DeMauro were responsible for genetic analyses and drafting that section of the manuscript. Kimmo J. Hatanpaa and Charles L. White III were responsible for the pathologic analysis of the APBD + FTL-D-TDP patient. Qinwen Mao and all other authors were responsible for critical analysis and revision of the manuscript. Authors have no conflict of interest with this work.

APBD is an autosomal recessive or sporadic progressive neurologic disease characterized by the diffuse accumulation of abnormally branched glycogen in polyglucosan bodies (PBs) [2, 3]. Patients generally present in their fifth to seventh decades with neurogenic bladder and motor neuron dysfunction, and sometimes dementia, peripheral neuropathy, and cerebellar dysfunction [2–4]. APBD may present with frontotemporal dementia (FTD) [5]. Familial APBD due to mutations in the glycogen branching enzyme gene (*GBE1*) was initially described in Ashkenazi Jewish patients [4]. A substantial percentage of individuals with APBD harbor a single mutation in one *GBE1* allele [4–6]. Manifesting heterozygous individuals may have undetected mutations affecting *GBE1* transcription, or mutations in another gene that may act synergistically with the mutated *GBE1* allele to produce APBD [3]. Mutations have been discovered in other populations and today APBD is considered a pan-ethnic disease [6].

Frontotemporal lobar degeneration (FTLD) is more common, with prevalence in those under age 65 equal to that of Alzheimer disease. In most cases, there are aggregates of abnormal tau (FTLD-tau) or TDP-43 (FTLD-TDP) [7]. Approximately 10% instead demonstrate aggregates of abnormal fused in sarcoma (FUS) protein (FTLD-FUS) [7, 8]. There are three main FTLD-FUS subtypes, including atypical FTLD-U (aFTLD-U), neuronal intermediate filament inclusion disease, and basophilic inclusion body disease [8]. Clinically, patients present with **bvFTD**, progressive primary aphasia, motor dysfunction, or a combination of these findings [8].

Clinical and pathologic analyses of all subjects were performed under IRB-approved protocols at the respective institutions.

A 35-year-old Caucasian woman presented to neurology with a 2–3 year history of altered cognition and personality. She had no history of learning disability or dyslexia, graduated from college, and worked until age 32 when she became disabled.

Initial symptoms included apathy, obsessive/compulsive behavior, and inattention. With no prior criminal history, she was twice apprehended for shoplifting. She was living in a skilled nursing facility, requiring assistance for all activities of daily living. She was not oriented to time or location, but was able to recall 3 objects after two minutes, and two after 5 minutes. Cranial nerves II–XII were normal. She moved all extremities with ease, and there was no focal weakness, ataxia, or gait abnormality. Brain imaging demonstrated significant atrophy involving bilateral frontal cortex and temporal poles. Laboratory tests were normal. There was no family history of psychiatric or neurologic disorders; the family was not of Ashkenazi Jewish heritage.

Seven months later she developed palmar grasp responses. She scored a 4 on the Folstein Mini-Mental State Exam, likely due to attention and executive function deficits. Ten months later she could no longer follow commands. Her only verbal output was to say her first name. Gait was stable.

She was seen for the last time 2 ½ years after her initial visit. Examination showed no extrapyramidal signs and gait was steady. The final clinical diagnosis was bvFTD. She died at age 41, after 8 years of disease, and a brain-only autopsy was performed.

The brain weighed 910 grams. Gross examination revealed severe atrophy of bilateral frontal and anterior temporal lobes, caudate nuclei and anterior hippocampus.

Histologic sections revealed severe neuronal loss and gliosis in neocortex and subcortical nuclei. Superficial neocortical microvacuolation was most prominent in frontal lobes and insular cortex. Numerous PBs were present in cortex and white matter, more severe in frontal and temporal cortex, and less numerous in subcortical regions, cerebellum, and brainstem. In white matter PBs were distributed diffusely rather than localizing to subependymal, perivascular and periventricular regions. PBs were pale gray-blue on hematoxylin and eosin stains; more were highlighted with periodic acid Schiff (PAS) (Fig. 1A), which revealed characteristic lamellated structure. PBs were also labeled by ubiquitin (rabbit polyclonal, 1:1000, DAKO, Carpinteria CA) (Fig. 1B). In addition, there were sparse round cytoplasmic inclusions in the hippocampal dentate gyrus, faintly labeled by ubiquitin and negative for neurofilament (SMI 31, 1:1000, Covance, Princeton NJ) and TDP-43 (pS409/410-2, 1:5000, CosmoBio, Carlsbad CA and rabbit polyclonal TDP-43, 1:500, ProteinTech, Chicago IL), but positive for FUS (rabbit polyclonal, 1:200, Protein Tech, Chicago IL) protein (Fig. 1C). FUS highlighted more inclusions than did ubiquitin, and revealed vermiform intranuclear inclusions not seen with ubiquitin, consistent with the pathology of FTLN-FUS, atypical FTLN-U subtype (FTLN-FUS, aFTLN-U) (Fig. 1D). In frontal cortex, FUS highlighted similar inclusions but did not label PBs. FUS inclusions were sparse in most cortical regions except parietal where they were moderate. The pathology was consistent with combined APBD and FTLN-FUS, aFTLN-U.

DNA was extracted from antemortem blood for genetic analysis. The patient had a heterozygous intronic mutation in *GBE1*, IVS5+2C>T, following exon 5. The mutation alters a splice site in the gene, ultimately resulting in nonsense-mediated decay of the transcript and therefore haploinsufficiency. The overall *GBE1* activity in homogenized brain tissue was found to be approximately 58% of normal. The other *GBE1* allele was normal.

Additional analyses reveal an ApoE ε4 genotype of 3,3. Sequencing of *MAPT* revealed no mutations in exons 9–13 and the TAU haplotype was H1H2. Mutation analysis revealed no mutations in *GRN*, *FUS*, or *CHMP2B* [9].

After discovering this case of APBD with concomitant FTLN-FUS, three other cases of APBD were immunostained with antibodies to tau, FUS, and TDP-43. One of the three cases, a 72 year old Ashkenazi Jewish man with a ten-year history of dementia, whose sister also had APBD [2], exhibited FTLN-TDP (Fig. 2). This is the second reported case of concomitant FTLN-TDP and APBD [1].

PAS stains of 49 additional FTLN-TDP and three FTLN-FUS cases revealed scattered perivascular, subpial, or subependymal corpora amylacea (CA) in virtually all cases and rare cortical CA, most often perivascular but occasionally lying free in the cortex. Two cases had focal clusters of cortical CA that were of higher density than the occasional cortical CA observed in most cases. There were no additional cases with widespread CA.

GBE1 encodes glycogen branching enzyme, deficiency of which results in glycogen with abnormally branched chains that accumulates as PBs [6]. Morphologically and

ultrastructurally PBs are identical to CA, but are more numerous and diffuse. PBs range in size from 2 to 70 micrometers in diameter and are PAS-positive [3]. In this paper, we show that they are also labeled with ubiquitin. In APBD, PBs are present in neuronal processes and ultrastructurally are also seen at the ends of astrocytic processes [10]. Disease is presumed to be due to the physical blockage of axons [10]. Approximately half to two-thirds of patients with APBD have cognitive impairment, and there is one report of APBD presenting with FTD [4, 5]. Antemortem sural nerve or skin biopsy can define the diagnosis, as PBs accumulate in axons and in myoepithelial cells of apocrine glands [3].

Clearly in this patient with bvFTD, APBD was not clinically suspected. However, it is not clear whether FTLT-FUS or APBD contributed more to the bvFTD in this patient. The density of PBs was greatest in the frontal and insular cortex, correlating with behavior impairment, while the density of FUS inclusions was greatest in the parietal cortex, suggesting that the distribution of PBs correlated better with the clinical syndrome. However, *GBE1* expression in this case was 58% of normal, and most *GBE1* heterozygotes with detectable enzyme activity are asymptomatic; on the other hand, rare manifesting heterozygotes have been reported [4].

Subsequent analysis of 52 additional FTLT cases revealed two cases of FTLT-TDP with focal clusters of moderate cortical CA, whereas the remaining 50 cases had only occasional cortical CA. The fact that CA were focal makes the diagnosis of concomitant APBD unlikely, but it may also imply the existence of a spectrum of CA density, ranging from mild perivascular, subependymal, and subpial to frank APBD. If APBD is considered, PAS or ubiquitin stains may be helpful. If frozen tissue is available, *GBE1* mutation analysis could be considered. When diffuse high densities of CA are seen the diagnosis of APBD can be made with confidence. However, the two cases with focal increased CA highlight the fact that diagnosing APBD on morphologic grounds alone can be problematic. Specific pathology criteria for APBD are needed, but are beyond the scope of this paper.

Brain autopsy revealed the first reported case of combined FTLT-FUS and APBD, and the first combined case with genetically-confirmed APBD. We also found a second case of combined APBD and FTLT-TDP [1]. Although these are only three cases, because APBD is rare, it is possible that APBD with concomitant FTLT is not uncommon. The reverse may not be true, however, because concomitant APBD was not definitively found in 52 additional cases of FTLT.

Acknowledgments

This study was supported in part by NIH P30 AG13854 (EHB, SW, MM), R01NS065782 (RR), and NIH P30 AG12300 (KH, CLW). We gratefully acknowledge the expert technical assistance of Annie Koronkiewicz and Melanie Peterson.

References

1. Farmer JG, Crain BJ, Harris BT, Turner RS. Coexisting adult polyglucosan body disease with frontotemporal lobar degeneration with transactivation response DNA-binding protein-43 (TDP-43)-positive neuronal inclusions. *Neurocase*. 2013; 19:65–75.

2. Suzuki K, David E, Kutschman B. Presenile dementia with “Lafora-like” intraneuronal inclusions. *Arch Neurol.* 1971; 25:69–80. [PubMed: 4111956]
3. Bigio EH, Weiner MF, Bonte FJ, White CL. Familial dementia due to adult polyglucosan body disease. *Clin Neuropathol.* 1997; 16:227–234. [PubMed: 9266150]
4. Ubogu EE, Hong ST, Akman HO, Dimauro S, Katirji B, Preston DC, Shapiro BE. Adult polyglucosan body disease: a case report of a manifesting heterozygote. *Muscle Nerve.* 2005; 32:675–681. [PubMed: 16007674]
5. Boulan-Predseil P, Vital A, Brochet B, Darriet D, Henry P, Vital C. Dementia of frontal lobe type due to adult polyglucosan body disease. *J Neurol.* 1995; 242:512–516. [PubMed: 8530979]
6. Hussain A, Armistead J, Gushulak L, Kruck C, Pind S, Triggs-Raine B, Natowicz MR. The adult polyglucosan body disease mutation GBE1 c.1076A>C occurs at high frequency in persons of Ashkenazi Jewish background. *Biochem Biophys Res Commun.* 2012; 426:286–288. [PubMed: 22943850]
7. Mackenzie IR, Neumann M, Bigio EH, Cairns NJ, Alafuzoff I, Kriol J, Kovacs GG, Ghetti B, Halliday G, Holm IE, Ince PG, Kamphorst W, Revesz T, Rozemuller AJM, Kumar-Singh S, Akiyama H, Baborie A, Spina S, Dickson DW, Trojanowski JQ, Mann DMA. Nomenclature and nosology for neuropathologic subtypes of frontotemporal lobar degeneration: an update. *Acta Neuropathol.* 2010; 119:1–4. [PubMed: 19924424]
8. Mackenzie IR, Munoz DG, Kusaka H, Yokota O, Ishihara K, Roeber S, Kretzschmar HA, Cairns NJ, Neumann M. Distinct pathological subtypes of FTL-D-FUS. *Acta Neuropathol.* 2011; 121:207–218. [PubMed: 21052700]
9. Urwin H, Josephs KA, Rohrer JD, Mackenzie IR, Neumann M, Authier A, Seelaar H, Van Swieten JC, Brown JM, Johannsen P, Nielsen JE, Holm IE, FReJA Consortium. Dickson DW, Rademakers R, Graff-Radford NR, Parisi JE, Petersen RC, Hatanpaa KJ, White CL III, Weiner MF, Geser F, Van Deerlin VM, Trojanowski JQ, Miller BL, Seeley WW, van der Zee J, Kumar-Singh S, Engelborghs S, De Deyn PP, Van Broeckhoven C, Bigio EH, Deng H-X, Halliday GM, Kriol JJ, David G, Munoz DG, Mann DM, Pickering-Brown SM, Doodeman V, Adamson G, Ghazi-Noori S, Fisher EMC, Holton JL, Revesz T, Rossor MN, Collinge J, Simon Mead S, Isaacs AM. FUS pathology defines the majority of tau-and TDP-43-negative frontotemporal lobar degeneration. *Acta Neuropathol.* 2010; 120:33–41. [PubMed: 20490813]
10. Dainese L, Monin ML, Demeret S, Brochier G, Froissart R, Spraul A, Schiffman R, Seilhean D, Mochel F. Abnormal glycogen in astrocytes is sufficient to cause adult polyglucosan body disease. *Gene.* 2013; 515:376–379. [PubMed: 23266647]

Fig. 1. APBD + FTLD-FUS

Numerous PBs highlighted magenta by periodic acid Schiff (PAS) stain of superficial frontal cortex (A) and ubiquitin immunohistochemistry (B). Hippocampal dentate gyrus with FUS immunolabeled neuronal cytoplasmic inclusions (NCIs) (C) and vermiform neuronal intranuclear inclusions (NIIs) (D, arrows). Arrowhead in D labels an NCI. Luxol fast blue / PAS stain, 400x (A), ubiquitin immunostain, 200x (B), FUS immunostains, 600x (C & D).

Fig. 2. APBD + FTLD-TDP

Superficial temporal cortex with TDP-43 positive NCI (arrowhead) and NII (arrow); TDP-43 positive short dystrophic neurites are also present (A). TDP-43 positive NCI in hippocampal dentate gyrus (B). TDP-43 immunostains, 600x.

Table 1

Regional densities of polyglucosan bodies and FUS positive inclusions

Brain Region	Polyglucosan bodies	FUS inclusions
Frontal cortex (BA8-9)	+++	+
Insular cortex	++	+
Superior temporal gyrus (BA22)	++	+
Parietal cortex (BA39-40)	+	++
Occipital cortex (BA17)	+	+

+ = sparse, ++ = moderate, +++ = frequent