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Coexisting adult polyglucosan body disease with frontotemporal lobar degeneration with transactivation response DNA-binding protein-43 (TDP-43)-positive neuronal inclusions

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Abstract

Frontotemporal lobar degeneration with ubiquitin-positive inclusions (FTLD-U) is one of the most common pathologic findings associated with the clinical FTLD syndromes. However, molecular characterization with genetic sequencing and protein expression techniques are recognizing many new subtypes for FTLDs. FTLDs are diverse, and new nomenclature schemes have been proposed based on the molecular defects that are being discovered (Mackenzie, 2010). Adult polyglucosan body disease (APBD) is a very rare disorder associated with systemic neurologic signs and symptoms including progressive dementia with executive dysfunction and motor neuron disease. We report the clinical course of an individual with a clinical FTLD and the as yet unreported findings of coexistent APBD with FTLD-U and transactivation response DNA-binding protein-43 (TDP-43)-positive inclusions at autopsy (or more accurately, FTLD-TDP). It is unclear if these distinct findings are coincidental in this individual, or if pathogenic pathways may intersect to promote these coexisting pathologies.

Keywords

dementia; frontotemporal lobar degeneration; transactivation response DNA-binding protein-43; TDP-43; ubiquitin; polyglucosan body disease; neuropathology

The frontotemporal lobar dementias (FTLD) consist of several disorders with overlapping nosology based on distinct clinical and neuropathologic features. These syndromes encompass behavioral variant FTLD, semantic dementia, progressive nonfluent aphasia, corticobasal degeneration, progressive supranuclear palsy, FTLD with Pick bodies, sporadic multisystem tauopathy with dementia, argyrophilic grain disease, neurofibrillary tangle dementia, FTLD with Parkinsonian features, and FTLD with ubiquitin-positive inclusions (FTLD-U), with or without motor neuron disease. Recent pathologic classifications distinguished syndromes based on tau-positive or ubiquitin-positive tau-negative inclusions (Cairns, Bigio, & Mackenzie, 2007). FTLD-U accounts for approximately half of all FTLD cases. Since 2006, distinction is based on whether inclusions are tau-positive or TDP-43-positive to define FTLD-tau and FTLD-TDP-43 (Cairns, Bigio, & Mackenzie, 2007; Chen-

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Plotkin, Lee, & Trojanowski, 2010). The most recent proposed nomenclature utilizes molecular classifications of FTLT-tau, FTLT-TDP, FTLT-UPS (ubiquitin proteasome system), FTLT-FUS (fused in sarcoma), and FTLT-ni (no inclusions) with recognized subtypes within these classes (Mackenzie, 2010).

Adult polyglucosan body disease (APBD) is a rare disorder characterized by bowel and bladder dysfunction, upper and lower motor neuron findings, cognitive impairment, gait disturbance, and sensorimotor polyneuropathy although some individuals present with a progressive dementia with prominent executive dysfunction (Boulton-Predseil, Vital & Brochet, 1995; Sindern, Ziemssen & Podskarbi, 2003). We now report, for the first time, an individual with a clinical FTLT and coexistent neuropathologic diagnoses of APBD and FTLT-TDP.

Case description

A 54 year-old right-handed woman of non-Ashkenazi Jewish descent presented to a neurologist with a one-year history of progressive memory decline. She had been initially diagnosed with mild depression and treated with antidepressant medications but memory and cognitive problems persisted. She frequently became lost in familiar places and had difficulty reading and completing routine tasks. The patient lacked insight to her problems that were readily apparent to her family and her medical providers. There was no history of bowel or bladder dysfunction, falls, seizures, hallucinations, or fluctuations.

On initial examination she scored 24/30 points on the Mini-Mental State Examination (MMSE). Vital signs were normal. Her examiner noted considerable difficulty processing information, answering questions, and following complex commands. She also demonstrated apraxia with routine tasks (for example, pulling out pages from the checkbook register instead of the checkbook). Cranial nerves (including eye movements), motor and sensory systems, coordination, and gait were all normal. There was no evidence to suggest parkinsonism, sensorimotor polyneuropathy, motor neuron disease, or a cerebral infarct. There was no asymmetry noted on examination initially, although a mild intention tremor of the right hand was apparent as her disease progressed.

Her past medical history included an asymptomatic left basal ganglia lacunar infarct (found on a prior head CT obtained for evaluation of recent memory decline), borderline hypertension, and distant ovarian cyst removal, and lumbar laminectomy. Her medications included antidepressant medications, hormone replacement therapy, and aspirin daily. She completed advanced higher education and was subsequently employed as a diplomat. She lived with her husband, denied tobacco use, and consumed a glass of wine or scotch nightly. There was a positive family history of small strokes and Alzheimer disease in the patient's mother (with unclear age of onset); no other family members were affected with a neurologic or psychiatric disorder.

The patient underwent neuropsychological testing which was abnormal and revealed a verbal IQ of 103, a performance IQ of 68, and significant deficits in multiple cognitive domains including memory, executive function, language, visuospatial skills, and praxis/motor sequencing. A cerebral MRI, performed with and without gadolinium, revealed mild to moderate atrophy and prominent white matter changes (interpreted as small vessel ischemic changes). Routine blood tests (chemistry, blood counts), thyroid function tests, and vitamin B₁₂ were all normal; all other laboratory testing, including RPR, was normal/negative. She was diagnosed with a mild dementia due to probable Alzheimer's disease, prescribed a cholinesterase inhibitor, and enrolled in a study. She was therefore re-evaluated thoroughly and frequently -- at 1.5, 3, 6, 12, 18 and 20 months after initial presentation. A diagnosis of behavioral variant FTLT became more apparent as her dementia progressed

with worsening apraxia and executive dysfunction. Repeated MMSE, ADAS-Cognitive, and Activities of Daily Living scales documented her gradual and progressive decline in cognition, function, and behavior (Tables 1, 2, and 3). She exhibited significant decline over the course of 20 months follow-up -- first in executive function and praxis and then in language domains. Basic activities of daily living remained relatively preserved until the 18- and 20-month evaluations. Because the initial diagnosis was considered to be Alzheimer's disease and neither FTD nor APBN, genetic studies (for example tests for mutations in MAPT, PRGN, or GBE1) were not requested. EMG and sural nerve biopsy were not obtained as there were no signs or symptoms to suggest neuropathy or motor neuron disease as seen with APBN.

Post-mortem

The patient died at age 59, and a brain-only autopsy was performed. Informed consent for brain donation was obtained after clinical presentation, and her legal guardian re-consented upon death of the patient. All procedures and consent forms were reviewed and approved by an Institutional Review Board. Grossly, the brain weight was abnormal at 871 g (normal = 1050–1550 g). Severe frontal atrophy and moderate temporal atrophy were noted, worse on the right, as well as caudate atrophy, and were consistent with a clinical diagnosis of behavioral variant FTLN (Fig. 1A). The substantia nigra was well pigmented. Specimens were taken from fixed cortices, basal ganglia, basal forebrain, thalamus, hippocampus, entorhinal cortex, amygdala, brainstem, cerebellum, and cervical spinal cord for microscopic analyses including H&E and silver stains as well as immunohistochemistry for tau, α -synuclein, ubiquitin, TDP-43, and huntingtin.

Microscopic findings included marked pallor and rarefaction in the white matter (Fig. 1B) including brainstem tracts, and gliosis (Fig. 1C). There was also neuronal loss throughout the neocortex and caudate. Frequent polyglucosan bodies were noted diffusely throughout the cortex and white matter, including the brainstem, subiculum, middle frontal gyrus, superior and middle temporal gyrus, occipital lobe, cingulate gyrus, insula, amygdala, and cerebellum (Fig. 1C,D). There were no Lewy bodies, balloon cells, Pick bodies, neurofibrillary tangles, or amyloid plaques, and no amyloid angiopathy was noted. Ubiquitin and TDP-43 immunostaining revealed cytoplasmic and intranuclear inclusions with a lens-shaped or cat's eye appearance as described in Cairns, Bigio, Mackenzie, et al. (2007) (Fig. 2). Sections were negative for tau, α -synuclein, and huntingtin. Intranuclear ubiquitin-positive inclusions were seen most prominently in neurons of the middle frontal gyrus, striatum, and internal capsule. TDP-43 positive glial and neuronal inclusions were rare and *semi-quantitatively* scored (see legend in Table 4) in all sampled areas with the highest numbers identified in the amygdala, caudate, putamen, cingulate gyrus, middle frontal gyrus, and inferior parietal cortex (Table 4). Thus, microscopic examination of multiple brain regions and sections revealed two distinct neuropathologic diagnoses -- namely APBD and FTLN-TDP. This is the first reported case of both diseases coexisting within a single individual.

Discussion

FTLN is an umbrella term that captures distinct neurodegenerative and progressive dementias (Cairns, Neumann, Bigio, et al., 2007). FTLN is the etiology of approximately 20% of presenile dementias and may be characterized by behavioral disinhibition, executive dysfunction, progressive language dysfunction, with or without motor neuron disease (Cairns, Bigio, Mackenzie, et al., 2007; Davidson, Kelley, Mackenzie, et al., 2007). In this case prominent disinhibition was not noted, but she suffered from apathy, progressive executive dysfunction, apraxia, and, later, aphasia. Macroscopically, brains with FTLN

demonstrate focal atrophy of the frontal, temporal, or both lobes (as found in this case), as well as associated atrophy of the basal ganglia and often depigmentation of the substantia nigra (Cairns, Bigio, Mackenzie, et al., 2007).

The FTLN syndromes have been classified primarily based on distinct microscopic neuropathologic features – particularly tau-positive (FTLN-tau) or ubiquitin-positive (FTLN-U) inclusions found on brain sections. FTLN-U with tau-negative, ubiquitin-positive inclusions was the most common underlying pathology reported for the FTLN syndromes (Cairns, Bigio, & Mackenzie, 2007). More recently, further distinction within the FTLN-U category became possible with the discovery in 2006 of transactivation response DNA-binding protein-43 (TDP-43)-positive inclusions. TDP-43 is a nuclear protein responsible for exon skipping and transcriptional regulation. In patients with FTLN-U and TDP-43-positive pathology, this protein is abnormally phosphorylated, ubiquitinated, and accumulates in neurons of hippocampus, neocortex, and spinal cord (Cairns, Neumann, Bigio, et al., 2007). TDP-43 is now recognized as a major component of the inclusions in cases of sporadic or familial FTLN-U, with or without motor neuron disease (MND), and is also found in cases presenting with sporadic or familial amyotrophic lateral sclerosis (ALS) (Chen-Plotkin, Lee, & Trojanowski, 2010). The older nosology of FTLN-tau and FTLN-U has been largely supplanted by FTLN-tau and FTLN-TDP as the two more common pathologic diagnoses. The less common FTLN-UPS, FTLN-FUS, and FTLN-ni are also included in a recently proposed nomenclature (Mackenzie, 2010).

This case demonstrated APBD with coexisting FTLN-TDP pathologies. APBD is a rare autosomal recessive disorder characterized by diffuse central and peripheral nervous system dysfunction. APBD was first recognized in individuals of Ashkenazi Jewish heritage but recent cases are described outside of this population (Sindern, Ziemssen, Ziemssen, et al., 2003). The disease course typically includes progressive upper and lower motor neuron disease, gait disturbance, severe sensory and motor neuropathy, bowel and bladder dysfunction and, later, cognitive impairment. However some cases may present with a progressive dementia similar to that found in individuals with FTLN (Boulton-Predseil, Vital, Brochet, et al., 1995).

The etiology of APBD in the Ashkenazi Jewish population is a missense mutation in the glycogen-brancher enzyme (*GBE1*, or 1,4- α -glucan branching enzyme) encoded at chromosome 3p12, with subsequent reduced enzymatic activity. In contrast, in glycogen storage disease type IV, *GBE1* activity is undetectable, and this disorder presents with hepatic and/or neuromuscular disease. More recently, in the non-Ashkenazi population two novel missense mutations in *GBE1* are known. Clinical diagnosis is based on a strong clinical suspicion combined with a sural nerve and skin biopsy (Milde, Guccion, Kelly, et al., 2001). The hallmark of the pathologic diagnosis is the observation of polyglucosan bodies on microscopic analysis of tissue sections, but this may be deceiving as other disorders such as glycogen storage disease type IV and Lafora disease may demonstrate nearly identical inclusions (Milde, Guccion, Kelly, et al., 2001). White matter involvement in APBD may be extensive and is readily apparent on cerebral MRI (Berkhoff, Weiss, Schroth, Sturzenegger, 2001).

It is unclear which of these two disorders is primarily responsible for the clinical FTLN in this individual. Both neuropathologies likely contributed to the progressive signs and symptoms documented, and APBD and FTLN-TDP are equally viable primary neuropathologic diagnoses. As found in this case, some individuals with APBD present with a progressive dementia, with prominent frontal and executive dysfunction, in the absence of a significant peripheral neuropathy or motor neuron disease. The question remains as to whether these two distinct pathologies are merely coincidental, or whether they may

intersect, with one disease primary and one secondary. For example, TDP-43 dysfunction may directly or indirectly alter neuronal expression/activity of *GBE1*/glycogen-branching enzyme. Molecular studies may directly test this novel hypothesis. In cases of frank FTLTDP, APBD may be overlooked or perhaps reported as corpora amylacea of normal aging. Alternatively, secondary TDP-43-positive immunostaining is reported in several neurodegenerative disorders, including Alzheimer's disease, and some α -synucleinopathies and tauopathies (Chen-Plotkin, Lee, & Trojanowski, 2010) -- and now APBD. In this case, secondary TDP-43 aggregation may represent a more general indicator of neuronal morbidity -- similar to tau aggregation as neurofibrillary tangles in response to diverse primary insults. Cases diagnosed at autopsy with either APBD or FTLTDP should be further scrutinized for evidence of these potentially co-existent pathologies. Perhaps it is not coincidental that their clinical phenotypes (ranging from frontal dementia with executive dysfunction to motor neuron disease) and anatomic neuropathologies sometimes overlap, and that both pathologies coexist in this individual.

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Figure 1.

A) Coronal gross brain specimen displaying enlarged ventricles, generalized atrophy, and temporal atrophy more prominent on the left (right side of figure), B) Low power photomicrograph of left frontal centrum semiovale with white matter pallor (H&E stain, original magnification 20×), C, D) High power photomicrographs of white matter with diffuse polyglucosan bodies and reactive astrocytosis (original magnification 200×, C – H&E stain, D – ubiquitin immunohistochemistry).

Figure 2.

A) TDP-43 neuronal inclusions in frontal cortex (TDP-43 immunohistochemistry), B) Lens shaped or cat's eye inclusion in the caudate nucleus (ubiquitin immunohistochemistry). (magnification bar for both A and B – 10 μ m).

Table 1

Mini-mental state examination.

	Time Course							
	Baseline	6 weeks	3 Months	6 Months	12 Months	18 Months	20 Months	
MMSE								
Date	-	-	-	-	-	-	-	
Year								
Month	-	-	-	-	-	-	-	
Day	-	-	-	-	-	-	-	
Season		-	-	-		-	-	
Hospital						-	-	
Floor							-	
City					-	-	-	
County			-	-		-	-	
State						-	-	
Immediate Recall	3/3	3/3	3/3	3/3	3/3	3/3	-	
DLROW	-	-	-	-	-	-	-	
Delayed Recall	2/3	-	-	-	-	-	-	
Naming						-	-	
Repetition	+ word/phrase	+ word/phrase	-	-	+ word	-	-	
3 step command				1/3 steps correct	-	-	-	
Written Command	+ close your eyes	+ close your eyes	+ closer your eyes	+ close your eyes	-	-	-	
Sentence						-	-	
Design		-		-		-	-	
Total score	20/30	17/30	15/30	12/30	10/30	4/30	0/30	

A (–) indicates an incorrect response.

Table 2

ADAS Cognitive Behavior. Each cognitive behavior is tested with multiple tasks; the number completed correctly out of the total number of tasks is indicated. The tasks that were completed incorrectly are noted in parenthesis.

	Time Course							
	Baseline	6 Weeks	3 Months	6 Months	12 Months	18 Months	20 Months	
ADAS Cognitive Behavior								
Immediate Recall	10/30		3/30	0/30	No longer able to complete	No longer able to complete	No longer able to complete	
Commands	3/5 (3 step commands)		1/5 (2 & 3 step commands)	2/5 (3 step commands)	1/5 (2 & 3 step commands)	0/5 (1, 2 and 3 step commands)	1/5 (2 & 3 step commands)	
Construction Praxis	3/4 (cube)		3/4 (cube)	3/4 (cube)	3/4 (cube)	No longer able to complete	No longer able to complete	
Delayed Recall	3/10		3/10	0/10	No longer able to complete	No longer able to complete	No longer able to complete	
Naming	No Difficulty		12/17	14/17	13/17	2/17	No longer able to complete	
Ideational Praxis	4/5 (address envelope)		4/5 (address envelope)	4/5 (address envelope)	1/5 (unable to fold letter, put in envelope, seal it, address it)	No longer able to complete	No longer able to complete	
Orientation	4/8 (month, date, day, time)		3/8 (month, date, day, season, year)	3/8 (month, date, day, season, year)	2/8 (month, date, day, season, year, time)	1/8 (month, date, day, season, year, time, place)	No longer able to complete	
Word Recognition	13/24		No longer able to complete	No longer able to complete	No longer able to complete	No longer able to complete	No Longer able to complete	
Instructions	Severe		Severe	Severe	Severe	Severe	Severe	
Verbal Comprehension	Very Mild		Mild (3-5 instance of misunderstanding)	Moderate (requires several repetitions and rephrasing)	Moderate Severe (occasionally responds correctly to yes/no questions)	Moderately Severe	Moderately Severe	
Word Finding	None		None	None	None	Severe	Severe	
Language	None		None	None	Mild (trouble < 25% of time)	Severe	Severe	
Maze	2 Errors / 28 seconds		2 Errors / 70 Sec	No longer able to complete	No longer able to complete	No longer able to complete	No longer able to complete	
Number Cancellation	6 Errors		No longer able to complete	No longer able to complete	No longer able to complete	No longer able to complete	No longer able to complete	

Table 3

Activity of Daily Living Assessment.

	Time Course						
	Baseline	6 Week	3 Month	6 Month	12 Month	18 Month	20 Month
ADL Assessment							
Eating	+		+	+	+	+	+/- (eats with hands not utensils)
Walking	+		+	+	+	+	+
Toileting	+		+	+/- (supervision, no physical help)	+/- (supervision, no physical help)	+/- (needs physical help, still continent)	+/- (needs physical help, still continent)
Bathing	+		+/- (reminders needed)	+/- (needed some physical assistance)	+/- (needed some physical assistance)	- (total assistance needed)	- (total assistance needed)
Grooming	+		+	+	+	+/- (needs assistance)	- (total assistance needed)
Dressing	+		+	+/- (supervision)	+	- (total assistance needed)	- (total assistance needed)
Telephone	+		+/- (only answered phone)	- (did not initiate or answer phone)	- (did not initiate or answer phone)	- (did not initiate or answer phone)	- (no phone usage)
TV use	+		+	+	+	+/- (watches TV, does not discuss program)	+/- (watches TV, does not discuss program)
Conversation	+		+	+	+	- (rarely or never spoke)	- (rarely or never spoke)
Clear Table	+		+	-	+	+/- (needs physical help)	-
Make hot beverage	+		+/- (assistance w/ stove)	+	+/- (assistance w/ stove)	-	-
Cook	+		+/- (assistance w/ stove)	+/- (need extensive help)	- (obtained food without mixing or cooking)	-	-
Clean	+		+	+	+	+/- (with assistance)	-
Solo Excursion	-		-	-	-	-	-
Shopping	+		+	- (supervision)	- (supervision)	-	-
Pay appropriately	+		-	-	-	-	-
Keep Appointments	+		+	+/- (needed verbal reminders)	+/- (needed verbal reminders)	-	-
Participate in Hobby	+		+/- (with assistance)	+/- (with assistance)	+/- (with assistance)	+/- (with assistance)	-
Use appliances	+		+	+/- (with assistance)	+/- (with assistance)	-	-
Left Alone	-		-	-	-	-	-

\$watermark-text

\$watermark-text

\$watermark-text

		Time Course							
ADL Assessment		Baseline	6 Week	3 Month	6 Month	12 Month	18 Month	20 Month	
Read		+		+	+	-	-	-	
Write		-		-	+	-(only name)	-	-	

A (+) indicates no difficulty, (+/-) indicates some difficulty with description/qualification in parenthesis, and a (-) indicates inability to complete the activity.

Table 4

Semi-Quantification of TDP-43 Inclusions in Brain Regions. Glial and neuronal inclusions were scored independently by two experienced neuropathologists (BTH, BJC) and consensus reached upon review.

Brain region	Consensus score
Middle Frontal Gyrus	4
Inferior Parietal Cortex	4
Superior Middle Temporal Gyrus	3
Occipital Cortex	0
Cingulate Gyrus	4
Hippocampus – CA1	2
Hippocampus - Dentate	2
Subiculum	3
Entorhinal Cortex	2
Inferior Temporal Cortex	2
Amygdala	4
Basal Forebrain	1
Caudate	4
Putamen	4
Globus Pallidus	1
Thalamus	4
Subthalamic Nucleus	1
Substantia Nigra	1
Basis Pontis	0
Locus Coeruleus	1
Cerebellar Cortex	0
Dentate Nucleus	0
Inferior Olive	1
Hypoglossal Nucleus	0
Dorsal Nucleus Vagus	1
Spinal Cord	1

Scoring was as follows: 0 = no inclusions in low power field (lpf; 4× objective), 1 = Mild (sparse inclusion in lpf), 2 = Moderate (>1 inclusion in lpf), 3 = Severe (4 or more inclusions in lpf), 4 = Very severe (numerous inclusions in lpf).