

## Semantic Dementia and Motor Neuron Disease: Case Confirmation of TDP43 Pathology Associated with a Predominant Right Temporal Atrophy

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**Received:** April 24, 2017; **Published:** May 17, 2017

### Abstract

We report the case of a right-handed 75-year-old man with semantic dementia associated with motor neuron disease. He initially presented with difficulties finding proper names at the age of 71 years. Impairment of object naming and loss of word meanings developed 1 year after the onset and the patient progressively ceased all reading activities. Over the course of his last year, he then showed severe signs of upper and lower motor neurons degeneration, fulfilling the international diagnostic criteria for semantic dementia and for amyotrophic lateral sclerosis. Pathological examination disclosed severe atrophy circumscribed to the anterior part of the temporal lobes, predominating in the right hemisphere. Marked gliosis and vacuolization were observed in the temporal cortex, especially in the upper layers. Tar DNA-binding protein 43 (TDP-43) and ubiquitin-positive cytoplasmic inclusions were detected in the pyramidal neurons of the temporal cortex as well as in spinal motor neurons. The association between the behavioural form of frontotemporal lobe dementia and motor neuron disease (FTLD-MND) is well described. However, the co-occurrence of semantic dementia and amyotrophic lateral sclerosis has rarely been reported. As for other forms of FTLD-MND, neuropathological findings correspond to frontotemporal lobar degeneration with TDP-43 inclusions (FTLD-TDP).

**Keywords:** Semantic Dementia; Amyotrophic Lateral Sclerosis; TDP-43

### Abbreviations

ALS: Amyotrophic Lateral Sclerosis; SD: Semantic Dementia; FTLD-U: Frontotemporal Lobar Degeneration with Ubiquitin-Positive Inclusions; TDP-43: Tar DNA-Binding Protein 43; FTLD-TDP43: Frontotemporal Lobar Degeneration with TDP43 Positive Inclusions; FTLD-MND: Frontotemporal Lobar Degeneration with Motor Neuron Disease; MND: Motor Neuron Disease

### Introduction

Semantic dementia (SD) is one of the clinical variants of frontotemporal lobar degeneration (FTLD). Patients with SD perform poorly on any task that involves semantic memory, such as picture naming, category fluency, word-picture matching, defining and drawing concepts in relation to their names [1]. In contrast, repetition, simple calculation, phonology and grammar of spoken language are preserved [2-4]. Caregivers usually report impaired social functioning such as a lack of empathy and emotional coldness [5].

**Citation:** Jean-Christophe Bier, *et al.* "Semantic Dementia and Motor Neuron Disease: Case Confirmation of TDP43 Pathology Associated with a Predominant Right Temporal Atrophy". *EC Neurology* 6.3 (2017): 146-152.

A proportion of patients present with right greater than left lateralized atrophy, referred to as right SD, or right temporal variant FTLN [6]. Neuman *et al* reported that the accumulation of ubiquitinated, phosphorylated, and N-terminally truncated TDP-43 is implicated in cases of frontotemporal lobar degeneration with ubiquitin-positive inclusions (FTLD-U) with and without ALS. [7] and constitute an important group of FTLN now designated as FTLN-TDP [8]. Josephs and colleagues confirmed a unique association between FTLN with type C pathology (FTLD-TDP type C with a predominance of long thick dystrophic neurites in the neocortex and Pick body-like inclusions in the dentate granular cells of the hippocampus) and corticospinal tract degeneration, with this entity showing a predilection to involve the right temporal lobe [9].

Amyotrophic lateral sclerosis (ALS) is characterized by considerable heterogeneity regarding site of onset, degree of upper versus lower motor neuron involvement, and rate of motor progression [8,9]. Five to 10% of ALS cases associate some form of FTLN [10,11]. We report here the unusual association of right-lateralized SD and ALS in a case with neuropathologically confirmed FTLN-TDP.

**Case Report**

A 70-year old engineer starting to complain of a progressive loss of names and dates was evaluated at the clinic in 2005. He also reported some lack of words in conversations and had stopped reading books. Since his retirement in 1995, he had become more impatient with people around him.

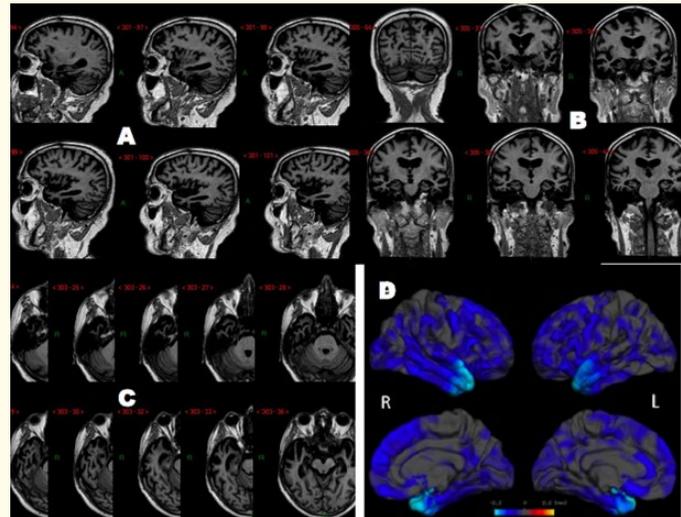
His Addenbrooke’s cognitive examination (ACE) [13] was 95/100 and the mini mental state examination (MMSE) was 30/30. A more exhaustive neuropsychological testing, conducted in 2008, revealed deficits during tasks of picture naming, verbal fluency, reading or writing irregular words, and verbal episodic memory (table 1). Both the word and picture versions of The Pyramid and Palm Tree test assessing semantic pairing abilities were impaired (table 1).

Test	01/2005	03/2006	10/2008
Digit span/ Block- tapping test	5/5	5/5	6/3
Verbal learning	Semantic encoding	16/16	16/16
	Immediate Recall	16/16	15/16
	Free Recall (3 trials)	8-9-9/16	8-10-12/16
	Cued Recall (3 trials)	<u>12-13-14/16</u>	12-11-14/16
	Delayed Free Recall	10/16	12/16
	Delayed Cued Recall	15/16	14/16
Fluencies in 2 minutes: P / Animals / Cued Animals	21/ 28/ND	20/24/ND	17/ <b>15/ 12</b>
Naming: Bachy-Langedock test	84/90 (2 MW)	<b>71/90</b> (10 MW)	<b>21/45</b> (24 MW)
PM38	47/60	ND	<b>21/48</b>
Picture learning: Doors Test (A+B)	ND	ND	<u>11/24</u>
Pyramid and Palm Tree - picture only / word only version	ND	ND	<b>30-28/40</b>
Reading/ writing irregular words	ND	ND	35/39 12/19
Calculation	ND	ND	14/14 5/5

**Table 1:** Neuropsychological evolution.

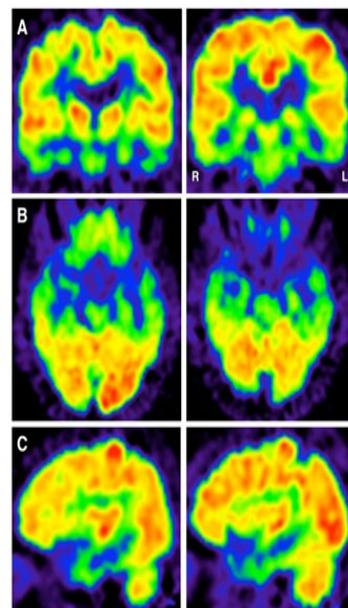
*ND: not done. MW: missing words. Significantly abnormal scores (more than 2 standard deviation from the given age and education normative data) are in Bold. Other scores that are equivalent to more than 1 standard deviation are underlined.*

It was regularly needed to repeat instructions and questions. Visuo-spatial abilities were preserved. Brain MRI revealed a diffuse cortical atrophy, predominantly in the temporal lobes (Figure 1) with concomitant profound and symmetric hypometabolism detected by FDG-PET (Figure 2).



**Figure 1:** Diffuse cortical atrophy, predominantly in the temporal lobes on MRI.

Sagittal (A), coronal (B), transverse (C); cerebral MRI T1 slices: diffuse cortical atrophy, especially in the temporal lobes. D: Quantitative analysis of cortical thickness relative to 10 age matched healthy controls: cortical atrophy more prominent in temporal lobes especially the right one (R: right, L: Left).



**Figure 2:** Cerebral FDG-PET.

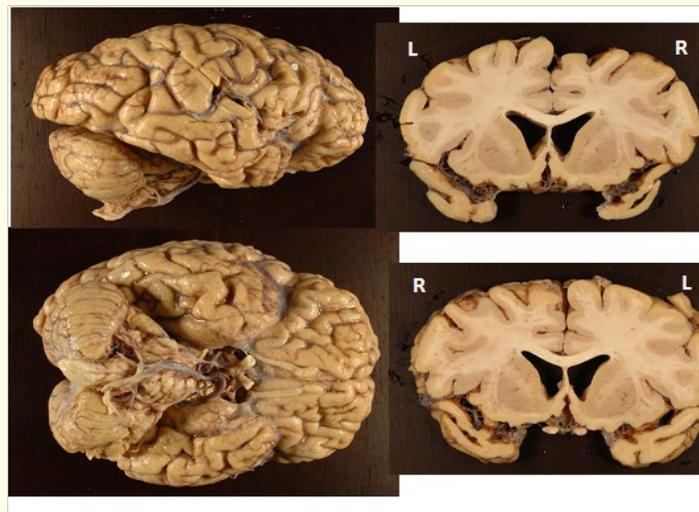
Coronal (A), transverse (B), sagittal (C) cerebral FDG-PET images showing bitemporal hypometabolism (R: right, L: Left).

His condition progressively declined over 2-year period, with difficulty in walking, causing several falls, and swallowing. At that time, neurological examination revealed the presence of logorrhea with motor and verbal perseverations. Verbal fluency and naming were impaired whereas language comprehension and repetition were preserved with a slight saccadic dysarthria. He had amyotrophy of the vastus medialis muscle and the interosseous of the hands. Evaluation of muscular strength decreased to 4/5 in the upper right limb, 4 +/ 5 in the upper left limb and 4/5 in the lower limb. Rapid fingers movements were slowed down. He had a hyperreflexia of all four limbs with extensor plantar reflexes. The masseter reflex was hyperactive. He presented fasciculations on all four limbs and in the tongue.

Coordination and sensory examination were normal for all modes of sensibilities. He died in June 2009.

### Neuropathological examination

The weight of the brain and spinal cord were 1230g and 42g, respectively. Meninges appeared normal. Both temporal lobes were atrophic, especially the right one. Frontal lobes were mildly atrophic (Figure 3).

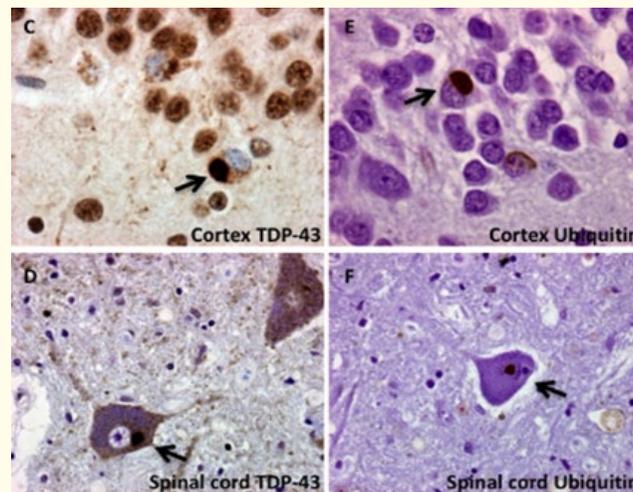


**Figure 3:** Macroscopic appearance of the brain: lateral view (A), basal ventral part (C) and coronal sections (B and D). Mild frontal lobes atrophy with severe atrophy in the anterior part of temporal lobes, more pronounced in the right (R) than in the left (L) hemisphere

*Mild frontal lobes atrophy with severe atrophy in the anterior part of temporal lobes, especially in the right hemisphere.*

Microscopic examination of the cortex showed an important atrophy of the cortical ribbon in the right and left temporal cortex. There was substantial vacuolization, neuronal loss, and GFAP positive astrocytic gliosis in the temporal cortex, more marked in the upper layers. Cytoplasmic inclusions immunoreactive for TDP-43 and for ubiquitin were identified in the neurons of the dentate gyrus. Many neurons without normal nuclear immunoreactivity for TDP-43 were also observed in the dentate gyrus, in pyramidal neurons in the Ammon horn and in the frontal cortex. Amyloid deposits were found in moderate quantity in the temporal and frontal cortices. A few rare neurofibrillary tangles in the transentorhinal cortex and in the frontal cortex were detected. There were no positive  $\alpha$ -synuclein inclusions

There was a partial discoloration of myelinated tracts (Luxol Fast Blue staining) of the lateral columns (corticospinal bundle), and a loss of motor neurons in the anterior horns of the spinal cord. Finally, cytoplasmic inclusions immunoreactive for TDP-43 and for ubiquitin were observed in some motor neurons in the anterior horns (figure 4).



**Figure 4:** Immunolabelling on tissue sections of the hippocampus (Dentate gyrus) (A and B) and of the spinal cord (anterior horn) (C and D), with antibodies to TDP-43 (A and C) and to ubiquitin (B and D).

*Histopathological images: TDP43 and ubiquitin positive cytoplasmic inclusions in pyramidal neurons of temporal cortex as well as in spinal motor neurons.*

## Discussion

SD appears to be one of the best characterized FTLT subtypes. SD begins with language dysfunction features and, with progression, affects behavior and social cognition. This reflects relatively circumscribed degeneration of the left anterior temporal pole, which encroaches into medial prefrontal and posterior temporal regions as well as into the contralateral hemisphere with disease progression. Pathologically, it is most commonly associated with TDP-43 type C inclusions. Familial forms due to genetic mutations are rare [15].

FTLD with motor neuron disease (FTLD-MND) is a distinct pathological entity, with neuropathological lesions characteristic of FTLT and MND, such as TDP-43 cytoplasmic inclusions and Bunina bodies (neuropathological hallmarks of ALS) [16]. While initially cognitively normal on evaluation, our patient eventually presented with clinical characteristics of SD. Within 3 years, he then developed motor neuron degeneration. Despite this, the association of SD with ALS has been relatively rarely reported. De Morsier, et al. reported a case of right-predominant temporal lobe atrophy and ALS in 1967. Clinical description of this study case, supports SD, except for its association to dyscalculia [17]. Kurachi, et al. also reported a case of right predominantly temporal lobe atrophy and ALS [18]. L.C. de Souza did so too with a case of DS associated to severe prosopagnosia and ALS developed in the 12 months [19]. Finally, Ostberg, et al. described a case of SD followed by ALS 7 years later, in which SPECT showed bitemporal hypoperfusion, yet predominant on the right side [20]. At the end of 2006, two independent groups identified TDP-43 as the component of cytoplasmic inclusions and dystrophic neurites in many cases of FTLT-U and ALS [21]. The case of SD associated to ALS that we report here actually has neuropathologically confirmed findings corresponding to FTLT-TDP with characteristic TDP-43 inclusions.

Our findings are consistent with studies in the literature reporting a right-predominant temporal lobe atrophy in some SD cases. This unusual case also stresses the fact that we should be more aware of motor disorders, in patients with right-lateralized SD.

## Conclusion

This case study with clinical, neuroimaging and neuropathological documentation confirms the association between right lateralized SD and ALS. This clinic-pathological entity seems to be associated with TDP-43 cytoplasmic inclusions, and right-predominant temporal lobe atrophy. Therefore, it is recommended to evaluate the motor system in patient with SD and right predominance of temporal atrophy.

## **Acknowledgements**

None.

## **Conflict of Interest**

None.

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**Volume 6 Issue 3 May 2017**

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