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Association atypique d'une démence sémantique, d'un syndrome cortico-basal et d'une tauopathie 4R

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RAPPORT DE SYNTHESE

ASSOCIATION ATYPIQUE D'UNE DEMENCE SEMANTIQUE, D'UN SYNDROME CORTICO-BASAL ET D'UNE TAUOPATHIE 4R

Enjeu et contexte de la recherche

La dégénérescence lobaire fronto-temporale (DLFT) est une pathologie neurodégénérative aussi fréquente que la maladie d'Alzheimer parmi les adultes de moins de 65 ans. Elle recouvre une constellation de syndromes neuropsychiatriques et moteurs dont les caractéristiques cliniques et anatomo-pathologiques se recoupent partiellement. La plupart des cas de démence sémantique ne présentent pas de troubles moteurs et révèlent à l'autopsie des lésions ubiquitine-positives. Son association à un syndrome cortico-basal et à une tauopathie 4R est donc très inhabituelle. Le cas que nous présentons est le premier à disposer d'une description clinique complète, tant sur le plan cognitif que moteur, et d'une analyse génétique et histopathologique.

Résumé de l'article

Il s'agit d'un homme de 57 ans, sans antécédents familiaux, présentant une démence sémantique accompagnée de symptômes inhabituels dans ce contexte, tels qu'une dysfonction exécutive et en mémoire épisodique, une désorientation spatiale et une dyscalculie. Le déclin physique et cognitif fut rapidement progressif. Une année et demie plus tard, il développait en effet des symptômes moteurs compatibles initialement avec un syndrome de Richardson, puis avec un syndrome cortico-basal. Son décès survint à l'âge de 60 ans des suites d'une pneumonie sur broncho-aspiration. L'autopsie cérébrale mit en évidence une perte neuronale et de nombreuses lésions tau-4R-positives dans les lobes frontaux, pariétaux et temporaux, les ganglions de la base et le tronc cérébral. Aucune mutation pathologique n'a été décelée dans le gène MAPT (microtubule-associated protein tau). L'ensemble de ces éléments sont discutés dans le cadre des connaissances actuelles sur la DLFT.

Conclusions et perspectives

Ce cas illustre le recoupement important des différents syndromes de la DLFT, parfois appelée le « complexe de Pick ». De plus, la démence sémantique pourrait s'avérer cliniquement moins homogène que prévu. Les définitions actuelles de la démence sémantique omettent la description des symptômes cognitifs extra-sémantiques malgré l'accumulation de preuves de leur existence. La faible prévalence de la démence sémantique, ainsi que des différences dans les examens neuropsychologiques, peuvent expliquer en partie la raison de cette omission. La variabilité histopathologique de chaque phénotype de DLFT peut également induire des différences dans leur expression clinique. Dans un domaine aussi mouvant que la DLFT, la co-occurrence ou la succession de plusieurs syndromes cliniques est en outre probablement la règle plutôt que l'exception.

ADDENDUM

Méthodologie de la recherche bibliographique

Le préalable a consisté en la consultation d'un ouvrage de référence (Hodges J.R. (2011), *Frontotemporal dementia syndromes*, Cambridge University Press, UK) et de la base UpToDate avec les mots-clés *frontotemporal dementia* afin de disposer d'un cadre théorique suffisamment large.

La recherche bibliographique électronique s'est poursuivie dans les bases de données Medline/Pubmed, Web of Science et Embase pour l'ensemble de l'article.
Les mots-clés *semantic dementia, primary aphasia, frontotemporal dementia, frontotemporal lobar degeneration, corticobasal degeneration, progressive supranuclear palsy, motor neuron disease, amyotrophic lateral sclerosis, tauopathy* ont été utilisés seuls ou en combinaison.
Les références ont été triées sur la base du titre et de l'abstract. La préférence a initialement été donnée aux articles publiés durant les 10 dernières années en anglais et en français, sans restriction géographique. La bibliographie de ces premiers articles a constitué une autre source de données.

Les critères de sélection ont été choisis en fonction des 4 catégories de références suivantes :
1) Pour les articles permettant la contextualisation du cas ou de certains aspects du cas, les revues récentes de la littérature et les consensus d'experts ont été privilégiés. De plus, les études cliniques les plus pertinentes, sur la base de la réputation du journal et du nombre d'articles et de citations des auteurs, ont permis d'élargir le propos, du cas présenté au cadre nosographique plus général.
2) Pour les articles décrivant une méthode ou une technique, les études de validation ou les ouvrages originaux décrivant les tests neuropsychologiques ont été listés. Les protocoles neuropathologiques ont été soumis pour approbation à M. Deprez, neuropathologue expérimenté et 2ème auteur. Comme l'analyse génétique était négative et que ce point n'allait pas être développé dans la discussion, seuls deux articles, apparus dans la recherche préliminaire avec le mot-clé *tauopathy* et reflétant l'état actuel des connaissances dans ce domaine, sont cités.

3) Les cas similaires publiés (3 *case reports*, 1 étude longitudinale, 1 *letter to the editors*) n'ont fait l'objet d'aucun filtre.
4) La discussion est basée sur la confrontation entre le cas présenté, les cas similaires publiés et les études récentes dans les domaines de la démence sémantique, la dégénérescence cortico-basale et les tauopathies. Le but de l'analyse a visé à aborder les aspects les plus significatifs du cas et à traiter de leurs principales interprétations en utilisant les connaissances antérieures accumulées par la recherche scientifique.
Les mêmes mots-clés et les mêmes critères de recherche qu'initialement ont été utilisés, mais en favorisant les articles originaux, études de cas et de cohorte, cas-témoins, séries de cas. Selon le sujet traité et lorsque des informations pointues faisaient défaut dans les articles déjà recensés, des mots-clés supplémentaires ont été adjoints aux premiers : *episodic memory, executive function, frontal dysfunction, apraxia of speech, orientation, spatial disorientation, calculation, dyscalculia, parkinsonism, extrapyramidal symptoms, imaging, neuropathology, etc.*
Trois critères d'inclusion ont été utilisés :

- le focus de l'article portait sur le point discuté (par ex. la mémoire épisodique dans la démence sémantique),
- le focus de l'article amenait un éclairage original sur le sujet,
- le focus de l'article permettait une comparaison avec le cas présenté.

Aucune restriction n'a été appliquée quant au design des études de façon à augmenter la sensibilité de la recherche bibliographique. Cette approche est justifiée par la rareté de la pathologie dans la population (pour mémoire, la prévalence globale des FTLD est estimée entre 2 et 35/100'000 personnes), par le nombre relativement élevé de formes de passage (*overlapping syndromes*) et par l'actuelle remise en cause des anciens cadres et définitions.

La possibilité de biais dans le traitement des références a été envisagée. Le biais de publication et « l'effet-tiroir » (*filedrawer effect*) sont difficiles à éviter dans les domaines scientifiques émergents. Les études présentant des conflits d'intérêt (biais d'allégeance) ont été écartées. Les biais de sélection et de confirmation sont amoindris par le recours systématique à la pluralité des sources et à la diversité des études. S'agissant de recherche qualitative, une approche intégrative a été utilisée. Elle a consisté en l'agrégation des différentes études en fonction de leur similarité afin de les regrouper en catégories (*pattern matching*), puis d'en faire la synthèse et d'obtenir une vue d'ensemble (*cross-case*

synthesis). Quatre à cinq études qualitatives de chaque catégorie ont été citées pour illustrer le propos (*explanation building*). Ce dernier a été comparé à la littérature existante dans le but d'augmenter la validité interne, la généralisation et le niveau théorique de l'étude de cas.

Le travail présenté est une étude de cas, et non une revue formelle de la littérature. Par conséquent, la méthodologie de la recherche bibliographique n'est pas l'objet de l'étude et ne figure pas dans l'article publié.

Le nombre d'articles passés en revue est par conséquent estimé a posteriori. La recherche par mots-clés a fourni environ 15'000 entrées qui ont été examinées sur la base du titre et de l'abstract, puis triées et sélectionnées selon les critères mentionnés pour ne retenir que les 131 références citées dans l'article, dont :

10 consensus d'experts
26 revues de la littérature
28 études de validation et ouvrages originaux décrivant les tests neuropsychologiques
18 case reports, multicentriques ou non
35 études comparatives, case series ou cas-témoins
12 études observationnelles de cohorte
1 letter to the editors
1 comment.

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Atypical association of semantic dementia, corticobasal syndrome and 4R tauopathy

Abstract : A 57-year-old male with no family history was diagnosed with semantic dementia (SD). He also showed some unusual cognitive features such as episodic memory and executive dysfunctions, spatial disorientation and dyscalculia. Rapidly progressive cognitive and physical decline occured. About 1.5 years later, he developped clinical features of a corticobasal syndrome (CBS). He died at the age of 60. Brain autopsy revealed numerous 4R-tau-positive lesions in the frontal, parietal and temporal lobes, basal ganglia and brainstem. Neuronal loss was severe in the temporal cortex. Such association of SD with tauopathy and CBS is highly unusual. These findings are discussed in the light of current knowledge about frontotemporal lobar degeneration.

Keywords : semantic dementia ; corticobasal syndrome; FTLD; tauopathy

Semantic dementia (SD) is one of the three prototypic neurobehavioral syndromes of frontotemporal lobar degeneration (FTLD), along with progressive nonfluent aphasia and behavioural variant of frontotemporal dementia (Neary, Snowden & Gustafson, 1998). FTLD syndromes overlap clinically, neuropathologically and genetically with three neurodegenerative motor disorders, i.e. corticobasal degeneration (CBD), progressive supranuclear palsy (PSP) and motor neuron disease (MND) (Boeve, 2007 ; Kertesz, McMonagle & Jesso, 2011). The neuropathological classification of the FTLD subtypes is based upon the specific types of intracellular protein inclusions and grouped into three major categories : FTLD-tau, FTLD-TDP (transactive-response DNA-binding protein 43) and FTLD-FUS (fused in sarcoma) (Mackenzie, Neumann & Bigio, 2010). A number of associated genes and mutations thereof have been identified, which may account for the relatively high rate of patients with a positive family history of FTLD or a related disorder (See, LaMarre & Lee, 2010; Goldman, Rademakers & Huey, 2011). Proposed clinicopathological correlations within the FTLD spectrum have proven to be frequently unreliable due to the phenotypic variability both at presentation and during the course of the disease (Boeve, 2007; Seelar, Rohrer & Pijnenburg, 2011; Rohrer, Lashley & Schott, 2011; Snowden, Thompson & Stopford, 2011). Indeed, the evolution of FTLD is characterized by the appearance of additional syndromes that differ from the initial clinical presentation, whether psychiatric or motor (Kertesz, McMonagle & Blair, 2005; Kertesz, Blair & McMonagle, 2007). Furthermore, each specific tissue pathology may cause multiple phenotypes (Weintraub & Mesulam, 2009; Rohrer et al, 2011). This considerable overlap may argue in favour of a single nosological entity, sometimes referred to as Pick complex (Kertesz, 2003; Kertesz et al, 2011). With respect to CBD, the clinicopathological heterogeneity has led many authors to use the term corticobasal syndrome (CBS) for the clinical disorder and corticobasal degeneration (CBD)

for the neuropathological diagnosis (Cordato, Halliday, & McCann, 2001; Boeve, 2011; Mathew, Bak, & Hodges, 2011).

SD is characterized by a loss of conceptual knowledge about words and objects. Core neuropsychological features include a fluent, empty spontaneous speech, loss of word meaning, semantic paraphasias, prosopagnosia and/or associative agnosia, preserved perceptual matching and drawing reproduction, preserved single-word repetition, preserved ability to read aloud and write to dictation orthographically regular words (Neary et al, 1998; Gorno-Tempini, Hillis & Weintraub, 2011). SD neuropathological analysis usually discloses an ubiquitin-positive TDP-positive pathology linked to MND, but several cases with tau-positive lesions due to microtubule-associated protein tau (MAPT) mutations, Pick's disease or Alzheimer's disease (AD) pathology have also been described (Davies, Hodges & Kril, 2005; Hodges & Patterson, 2007; Hodges, Mitchell & Dawson, 2010; Bessi, Bagnoli & Nacmias, 2010; Ishizuka, Nakamura & Ichiba, 2011; Snowden et al, 2011; Josephs, Hodges & Snowden, 2011; Rohrer et al, 2011). As a matter of fact, SD patients do not usually present any clinical motor disorder (Josephs et al, 2011; Kremen, Mendez & Tsai, 2011). Infrequent cases of clinical MND are briefly mentioned (Hodges et al, 2007; Ostberg & Bogdanovic, 2011). Some rare cases of concomitant SD and CBS/CBD have also been reported, though lacking neuropathological confirmation or detailed clinical description (Ikeda, Akiyama & Iritani, 1996 ; McMonagle, Blair & Kertesz, 2006 ; Raggi, Marcone & Iannaconne, 2007 ; Luzzi, Cafazzo & Silvestrini, 2012). One case of SD and neuropathological CBD, but without motor symptoms, has been published (Mathuranath, Xuereb & Bak, 2000).

Here we report the detailed case of a patient who presented initially with SD, later evolving into clinical CBS, whose brain autopsy revealed an atypical sporadic 4R tauopathy. Our

clinical, neuropsychological and neuropathological findings will be discussed in the light of the FTLD constellation.

METHODS

Neuropsychological testing

The patient underwent a longitudinal assessment which confirmed the progressive nature of his deficits. Neuropsychological testing was carried out in the memory clinic or at hospital by trained neuropsychologists. It consisted mostly of routine cognitive tests which have been described in detail elsewhere (for references, see Table 1). Arithmetic skills were not systematically addressed, but evaluated by means of the MMSE mental calculation and multi-digit written calculations (addition, subtraction or multiplication, with unlimited response time). The number of errors (for the MMSE task) is scored. The type of errors (for the written part) is assigned to three categories, i.e. comprehension of symbols (e.g. +/-), knowledge of arithmetic facts (e.g. multiplication tables) and application of procedures (Julien, Thompson, & Neary, 2008). Moreover, a locally developed semantic battery, designed to assess input to and output from semantic knowledge via different sensory modalities, was also administered. Indeed, many of the tests used in current clinical and research settings to investigate language and semantic memory were not available in French at the time of the study.

The first semantic test contains 36 items, chosen from a corpus of 260 line drawings (Snodgrass & Vanderwart, 1980), representing three categories of living items (fruit, vegetables, animals) and three categories of man-made items (clothes, tools, furniture) matched for familiarity and visual complexity. This test consists of several sub-tests. The patient is first asked to draw all 36 items by memory to evaluate semantic memory by a verbal input and a non-verbal output. Copy of a line drawing assesses visuoconstructive and

visuoperceptual skills. The patient then proceeds to naming all 36 line drawings without cueing (non-verbal input, verbal output). If unsuccessful, the patient is shown an array of six pictures chosen within the same category (e.g. animals) and asked to point to the target item named by the examiner (verbal and non-verbal input, non-verbal output). If designation fails, the patient is asked for a verbal definition. He then has to answer two probe questions concerning the same items, one to explore knowledge of perceptual features (shape, size, color, etc.), the other one to examine semantic knowledge of functional or contextual attributes (origin, diet, uses, etc.) (Chertkow, Bub, & Deaudon, 1997). These tasks provide evidence for possible single-word comprehension deficits and differentiate between storage degradation and failure of access to semantic knowledge (Hodges, Salmon, & Butters, 1992). Control data for similar tasks using 42 items have been elicited by the assessment of 65 healthy individuals (27 men, 38 women, between 15 and 70 of age): control-subjects answered correctly 98% of functional probe questions and 99% of perceptual probe questions (Rodriguez & Martory, 1998). Additionally, 98.5% of control drawings were identifiable, i.e. correct or presenting enough essential characteristics to be recognized in spite of missing or erroneous details. In absence of formal standardization and validation studies, scoring consists of a quantitative estimate of the patient's performance (mild, moderate, severe or no deficit). To improve readability of the results, raw scores have been presented in Tables 1 and 2 whenever possible. For items as "comprehension" or "verbal semantic memory", assessed by several sub-tests (definitions, probe questions, identification, etc.) and by clinical observation, a global evaluation was preferred. Examples and details of the patient's answers can be found in the Case report section.

Additionally, we used a shortened French version of the Boston Naming Test (BNT) which has been developed with 34-item (version A/B) or 20-item (version C/D) sub-tests standardized for age, years of education and gender (Thuillard Colombo & Assal, 1992). Cut-off points are 27/34 for version A/B and 14/20 for version C/D.

Moreover, semantic memory was assessed using a tactile input. Eyes closed, the patient was given real objects (e.g. scissors, pencil, apple, etc.) he had to name. In case of omission or error, perceptual and functional attributes were asked for. If still unsuccessful, the patient was allowed to look at the object and the same questions were asked again. We took into account the number and type of errors to give a qualitative estimate of the patient's answers. This succinct test differentiates tactile agnosia, tactile aphasia and loss of semantic knowledge.

Non-verbal semantic memory was assessed by a set of 13 photographs of seven famous faces and six famous buildings. The selected famous people were alive during the patient's lifetime and fell into two broad categories: actors (e.g. Charlie Chaplin) or politicians (e.g. Mikhail Gorbachev). Famous buildings from across the world (e.g. White House, Great Wall of China) were presented as colour pictures. The patient was shown each photograph and asked to name the person or the building, then to provide identifying information (e.g. former president of USSR). If impossible, the patient was administered a three-alternative task with semantically matched items (e.g. actors if the target item was an actor, cities if the target item was a building). Responses were considered correct if the full name was right. The verbal explanations or the multiple-choice task are meant as lenient criteria to compensate for the limited access to vocabulary and semantic knowledge. Then, the patient was told some famous names (persons and monuments) and asked for identifying information to allow further discrimination between prosopagnosia, anomia and semantic impairment. Indeed, a specific processing for famous faces, names and buildings has been established, with dedicated brain regions representing modality or category specific information (Gorno-Tempini & Price, 2001; Snoeden, Thompson & Neary, 2004). As previously, usual scoring consists of a qualitative evaluation of the patient's performance which is, however, presented as raw scores in Table 1 for the reader's convenience.

Language tasks whose semantic nature remains controversial such as reading aloud, repeating or writing to dictation, have been assessed using French words. The reading list comprised 24 words (one to four syllables) with 8 regular words, 12 irregular words and 4 pronounceable non-words which the patient had to read aloud. Next, the examiner read another list of 17 words and non-words (two to five syllables) one by one, asking the patient to repeat. Finally, the patient was asked to write to dictation a list of 15 regular, irregular and non words. The number (see Table 1) and type of errors (regularization, phonologically plausible or implausible errors) are considered relevant and were evaluated clinically according to current knowledge about primary progressive aphasia (Caine, Breen, & Patterson, 2009; Shim, Hurley, & Rogalski, 2012).

Neuropathology

Autopsy was performed within 48 h of death and the entire brain fixed in 10% formalin for 3 weeks. Tissue blocks were taken from the frontal, temporal, parietal and occipital lobes, hippocampus, midbrain, pons, medulla oblongata and cerebellum, accordingly to consensus protocols (Cairns, Bigio & Mackenzie, 2007 ; Dickson, Bergeron & Chin, 2002). These blocks were embedded in paraffin and sectioned at 6 µm. Sections were stained with hematoxylin and eosin, luxol fast blue and Gallyas silver method. Immunohistochemistry helped identifying the type and distribution of lesions, using antibodies against glial fibrillary acidic protein (6F2, M0761, Dako, Glostrup, DK, diluted 1 :1000), neurofilaments (2F11, M0762, Dako, Glostrup, DK, diluted 1 :6000), α-synuclein (KM51, NCL-ASYN, Leica, Newcastle, UK, diluted 1 :20), tau protein (tau-2, T5530, Sigma, St Louis, MO, diluted 1 :200), phosphorylated tau (AT8, Thermo Scientific, Rockford, USA, diluted 1:100), tau isoforms 3R (8E6/C11, Millipore, CA, USA, diluted 1:200) and 4R (1E1/A6, Millipore, CA, USA, diluted 1:200), α-B-crystallin (G2FJ, NCL-ABCrys-512, Leica, Newcastle, UK, diluted 1 :2400),

ubiquitin (Ubi-1, 08-0147, Invitrogen, Camarillo, CA, diluted 1 :1), TDP-43 (TARDBP Polyclonal antibody, Proteintech Europe, UK, diluted 1:500) and Aβ-amyloid (6F/3D, M0872, Dako, Glostrup, DK, diluted 1 :50). Neuropathological alterations (gliosis, neuronal loss and protein inclusions) were semiquantitatively evaluated using a four-point scale (none, mild, moderate, severe).

Genetics

The MAPT gene was analysed by polymerase chain reaction and sequencing of both DNA strands of the entire coding region and the highly conserved exon-intron splice junctions. In addition, multiplex ligation-dependent probe amplification analysis was performed to test for deletions or duplications of one or more entire exons within the gene (Spillantini, Van Swieten, & Goedert, 2000; Goedert & Spillantini, 2011).

CASE REPORT

A 57-year-old right-handed man with 13 years of education, unemployed for one year, was referred by his physician to the memory clinic. He had a 3-year history of insidious behavioural changes such as a narrowed range of interests, decreased drive and subsequent reduction in spare-time activities like reading, watching TV or visiting expositions. He complained of memory loss, especially remembering conversations or readings. His wife noticed an altered speech with a reduction of the panel of subjects he was able to discuss, as well as difficulties finding his words and understanding what was said. He had trouble recognizing faces of people he knew and identifying voices on the phone. He also did not seem to identify the ingredients she cooked, for instance asking if a salmon was meat. Although he had briefly worked as a taxi driver a couple of years ago, he had trouble finding his way in the city. He seemed unable to drive because of the many tasks he had to

handle simultaneously. An emotional instability was also described. Family history of mental illness disclosed that the patient's father died aged 86 of unconfirmed Alzheimer's disease. The patient's mother, aged 90, was living in a nursing home also due to presumed Alzheimer's disease. No other kindred were known to be ill.

The first out of four successive neuropsychological examinations was performed (Table 1). It revealed a logorrhoeic speech with semantic paraphasias, word-finding difficulties, digressions, thematic perseveration, without phonemic paraphasias, nor syntax errors. Apart from omissions ("I don't know"), naming errors were either within category (e.g. donkey for camel), superordinate (e.g. animal for octopus), circumlocutory (e.g. something to play tennis with for racket) or generic (e.g. thing). His score of 13/34 on the French version A of the BNT is considered a severe impairment. As for the other naming score of 22/36, the results were clinically appreciated in absence of normative data. However, 61% hit rate of correct answers corresponds to a largely insufficient performance. Repetition of single words and sentences was normal. The patient produced phonologically plausible (regularization) errors on reading and writing irregular words, a pattern described as surface dyslexia and dysgraphia. The results of the semantic test battery reflected the substantial impairment in semantic knowledge, affecting not only naming, but also fundamental aspects of living and man-made things. Comprehension deficits also were prominent for single words. The patient was not able to generate simple definitions ("What is a butterfly? It's a bird. It isn't like a fly, a fly doesn't have wings."), nor basic information about famous persons and places (e.g. picture of the Coliseum: "I don't know where it is. In Paris."). Drawings by memory, picture pointing, picture naming and probe questions indicated a clear-cut deficit for natural categories (Table 2). Drawings illustrated the striking dissociation between semantic memory (Figure 1) and visuoconstructive skills (Figure 2). Non-verbal tests of semantic knowledge disclosed a multimodal deficit. Tactile, as well as visual, face and/or object recognition were impaired (Table 1). The Lexis visual matching test (which consists of matching a picture with a

semantically associated one, e.g. musical instruments, among visual or semantic distractors) has been attempted, but failed due to the patient's inability to both understand the task and identify the target item (de Partz, Bilocq, & De Wilde, 2001). Written calculation was difficult due to procedural errors: smaller-from-larger subtraction, e.g. 87-9=82; omission of carry/borrow procedures, e.g. 39x5=155; partial-answers-separated, e.g. 39x4=1236. Oral calculation was also impaired (MMSE 3/5). Praxis, visuospatial and visuoperceptive skills were globally preserved (exceptions: imitation of one non-significant gesture needed the examiner's help to be achieved; patient drew both clock arms of the same size). Episodic memory was markedly impaired. Verbal memory testing had to be stopped after the first attempt of cued recall due to the patient's discouragement. Non-verbal memory tests confirmed severe deficits. Executive testing confirmed the clinically noticeable slowness and perseveration. Verbal fluency tests showed a greater reduction in semantic rather than letter-based categories. However, the patient was able to take care of himself and independent as for daily living. Brain magnetic resonance imaging (MRI) showed a moderate atrophy with left temporal lobe predominance (Figure 3). On neurological examination, the only pathological finding was an unextinguishable glabellar reflex.

Seven months later, a second neuropsychological assessment was performed. The results were limited by the patient's tendency to leave many tasks unfinished when he was unable to complete them correctly. He expressed his frustration by swearing to himself, sighing aloud and shaking his head. His speech was still digressive, repetitive and logorrhoeic in spite of a severe anomia. On writing a text to dictation, he made several phonologically plausible and non plausible errors (one omission, one substitution, one addition of a letter). Writing of regular single words and non-words was still preserved. Imitation of two out of four non-significant gestures needed the examiner's step-by-step demonstration to be achieved. Episodic memory could not be tested due to patient's refusal. He expressed growing difficulties of comprehension. He did not understand the purpose of the examination and kept

on believing he was going to get better as soon as he would find a new job. Insight was poor as evidenced by the lack of acknowledgment of any cognitive disorder, except for memory. Semantic memory slightly worsened as revealed by impaired naming of line-drawings and drawing by memory. In both tasks, natural categories were the most affected (e.g. cat similar to rabbit, both unidentifiable), but new difficulties had appeared concerning man-made items (e.g. sweater similar to overcoat). Pointing to pictures helped identification when words were lacking, but eventually the patient gave up the task. Neither definitions, nor probe questions could be asked. Executive functions also deteriorated. Information processing speed slowed. Shifting and attentional errors appeared during the Trail Making Test.

Eight months later, the patient was admitted to the psychiatric hospital due to suicidal thoughts and progression of the cognitive decline. The patient had lost autonomy in several activities of daily living (dressing, personal hygiene, money management, public transport, housework, medication). He presented marked psychomotor retardation, apathy, an inexpressive face and a staring gaze. His spontaneous speech had become scarce and laborious, with growing anomia. Nonetheless, it was his long-duration unemployment, rather than his cognitive impairment, that was the cause of his despair and suicidal thoughts. The patient still had little awareness of his difficulties. The third neuropsychological examination confirmed the worsened performances. Regularization errors on reading increased in number, as did phonologically plausible and implausible errors on writing (same type of errors as previously). Written calculation was preserved for the simplest operations (addition and subtraction without carry/borrow procedures), but had become impossible for multi-digit multiplication due to complete loss of procedure. Identification of overlapping figures required the examiner's help, indicating the contours of the items, to be achieved. Speed of information processing had slowed. Trail Making Test part B was stopped after four minutes due to the patient's failure to complete the task. Episodic and semantic memory had worsened. The semantic battery had to be adapted to the patient's disability. Naming was

restricted to 6 items (one per category, score 4/6), as was drawing by memory (no identifiable items). None of the definitions was adequate (e.g. “A frog is a tool, isn’t it?”). Five out of ten probe questions were answered correctly (3/5 perceptual, 2/5 functional). Naming score had dropped to 6/20 on the BNT version D. As pointed out by these tests, verbal and non-verbal comprehension had deteriorated. After a one-month stay, the patient was sent back home. During the following months, his cognitive state deteriorated considerably. He stopped his daily walks after getting lost a few hundred meters away from home. He became dependant for all activities of daily living, unconcerned by his environment, apathetic and submissive. The patient no longer complained about anything, seemingly insensible to his own condition. He even reported feeling happy apart from being unemployed. No socially inappropriate behaviour was present.

Gait disorders appeared six months later, causing several falls which led to his second hospitalisation. By that time, the patient had developed urinary incontinence. Neurological examination showed a wide-based, small-stepped and unsteady gait, bradykinesia, axial greater than limb rigidity with a right-sided predominance, dystonic head position towards right, tendency to backwards falls, vertical gaze palsy, reduced blink reflex, hypomimia, palmar grasp reflex, environmental dependency syndrome (utilization and imitation behavior) and marked psychomotor slowing. There were no myoclonus or fasciculations. Structural brain MRI (Figure 4) revealed a severe, left greater than right cortical atrophy of the temporal and parietal lobes, predominantly affecting the temporal poles, hippocampus and amygdala. Increased signal intensity changes in T2-weighted images were noted in the temporal subcortical white matter on both sides. Atrophy of the frontal lobes was symmetrical. Occipital lobes were spared. A marked atrophy of the pons, midbrain tegmentum and cerebral peduncles was patent, with a hummingbird sign on the sagittal images. No thinning of the corpus callosum was observed. A moderate atrophy of the cerebellar hemispheres, with preserved vermis and cerebellar peduncles, was present. The last neuropsychological

assessment showed newly acquired disorientation for time and place. Frontal dysfunction had increased as evidenced by the considerable slowing, echolalia and grasp reflex. Bucco-facial gestures and identification of overlapping figures proved impossible to perform. The deterioration of the language, both receptive and expressive, was tremendous. Speech needed strong encouragement and consisted of isolated words. Even real objects could not be named, nor identified. Well rehearsed ordered series, like the days of the week or the months of the year, were preserved. Simple written and oral orders (e.g. close your eyes) were understood, but not closed-ended questions (e.g. is it sunny today?). Repetition of regular and irregular words remained possible, which was not the case of non-words. Greatly impaired comprehension and motor disability prevented further testing. Within a few months, the patient's clinical state dramatically worsened. He developed right spasticity with neck and upper limb predominance, antecollis, was no longer able to walk or talk, became mute, wheelchair bound and finally bedridden. Several episodes of seizure-like absence with dyspnea, cyanosis and diaphoresis occurred. Electroencephalography showed an inconspicuous left-sided lateralization without irritative components. Ultimately, the patient developed dysphagia, complicated by aspiration pneumonia of which he died at age 60.

RESULTS

The entire brain weighted 1250 g. Macroscopic examination showed atrophy of the midbrain as well as the frontal, temporal and parietal lobes with ex vacuo ventricular dilatation. Microscopically, cortical lesions were characterized by neuronal and axonal loss, gliosis and spongiosis of varying severity: they were mild in the parietal and occipital cortices, moderate in the frontal cortex and extreme in the temporal lobes and hippocampus, leading to devastation of the laminar pattern of the cortex (Table 3). Innumerable 4R-tau-positive neuronal and glial inclusions were present as neurofibrillary tangles, pre-tangles, neuropil

threads, astrocytic plaques and oligodendroglial coiled bodies (Fig 5a-f). These tau-immunoreactive inclusions were particularly abundant in the frontal, parietal and temporal cortices. The hippocampus showed marked accumulations in the dentate gyrus, Ammon's horn, subiculum and entorhinal cortex. Many spherical cytoplasmic inclusions in the granule cell layer of the dentate gyrus, reminiscent of Pick bodies, revealed to be strictly 4R immunoreactive. Basal ganglia (caudate nucleus, putamen, globus pallidus, subthalamic nucleus, substantia nigra) and basal nucleus of Meynert all contained numerous tau-positive glial lesions with little neuronal loss and neuronal inclusions. Striatum and globus pallidus contained mostly glial inclusions, whereas thalamus and inferior olivary nuclei showed chiefly neuronal inclusions. Midbrain showed marked widespread tau-positive lesions and moderate depigmentation and neuronal loss in the substantia nigra. Cranial nerves nuclei and medullary gray matter were midly involved. Cerebellar dentate nucleus had moderate inclusions associated with mild grumose degeneration. Subcortical white matter was extensively and severely affected.

Achromatic ballooned neurons were scarce and positive to neurofilaments and 4R tau immunohistochemistry. No tufted astrocytes, nor classical Pick bodies were observed. Immunostaining was negative for α-B-crystallin, α-synuclein, TDP-43, Aβ-amyloid and inconsistently positive for ubiquitin and 3R tau. The 4R-tau-positive inclusions proved to be heterogeneously sensitive to Gallyas staining : they were negative in neurons, faintly positive in astrocytes and clearly positive in oligodendrocytes and threads.

No pathological mutation was found in the MAPT gene.

DISCUSSION

The case we report presented initially with fluent speech, severe progressive anomia, impaired naming and single-word comprehension, impaired verbal and non-verbal semantic memory, manifest in failure of face and object recognition, different forms of agnosia (visual and other modalities agnosia, prosopagnosia, anosognosia), surface dyslexia and dysgraphia, semantic paraphasias, manifesting a profound multimodal loss of semantic knowledge. Syntax and phonology were preserved, as were drawing reproduction, single-word repetition, ability to read aloud and write to dictation orthographically regular words. These traits, along with behavioral changes and supportive brain imaging at the time of diagnosis, are consistent with all the core diagnostic features and most of the supportive ones according to Neary's criteria of SD, and with all Gorno-Tempini's inclusion criteria (Neary et al, 1998; Gorno-Tempini et al, 2011). Whereas SD language deficits are duly listed in both definitions, the non-semantic aspects of the disease are omitted, except as exclusion criteria. These have changed over time due to the growing amount of evidence and will probably undergo further updating. Our review of the literature provides support to the current opinion that SD non-semantic deficits may have been previously overlooked. As discussed below, apart from his prominent initial semantic impairment, our patient also showed a number of unusual cognitive, motor and neuropathological features.

Episodic memory was altered, an uncommon finding in the initial clinical picture of SD (Neary et al, 1998; Hodges et al, 2007; Harciarek & Kertesz, 2011). With progression over time, however, it is now accepted that episodic memory declines in SD as a function of the disease severity (Grossman, Xie & Libon, 2008; Matuszewski, Piolino & Belliard, 2009; Xie, Libon & Wang, 2010; Chrysikou, Giovannetti & Wambach, 2011). In our patient, diagnosis of SD follows disease onset by three years due to late referral, with concomitant disease progression. Accordingly to current data indicating a median survival of 6-11 years from symptom onset and 3-4 years from diagnosis, our patient should be considered an intermediate to late-staged SD (Rabinovici et al, 2010; Hodges et al, 2010). Secondly,

growing evidence highlights some under-recognized cognitive features in SD, most notably episodic memory impairment, even at presentation (Thompson, Patterson, & Hodges, 2003; Scahill, Hodges, & Graham, 2005; Söderlund, Black, & Miller, 2008; Chan, Anderson, & Pijnenburg, 2009; Pleizier, van der Vlies, & Koedam, 2012; Irish & Piguet, 2013). Current SD criteria may account for the low rate of reported cases or lead to incomplete cognitive testing. None of the formerly reported SD-CBD cases mentions the presence of episodic memory impairment (Table 4). At a closer look, though, one of the patients reveals poor memory scores at the initial assessment (Mathuranath et al, 2000). Thirdly, in the domain of episodic memory, MMSE total score and recall sub-score do not differ between FTLD, SD and AD patients (Grossman et al, 2008; Shimizu et al, 2011). These data seem therefore rather irrelevant to describe SD diagnosis and course. Fourthly, nonverbal episodic memory in SD has proven to rely heavily upon perceptual inputs to medial temporal memory structures (Graham, Simons, & Pratt, 2000; Simons, Graham, & Galton, 2001). The hypothesis is that SD patients may not be able to encode new information when perceptually different. Fifthly, the hippocampal complex, once thought to be spared in SD, may actually show a substantial atrophy, sometimes even greater than in AD patients matched for disease duration (Hodges & Miller, 2001; Davies, Graham, & Xuereb, 2004; Söderlund et al, 2008; Pleizier et al, 2012). All these interesting observations should warrant caution against SD overly restrictive criteria and point to the need for their future revision. On the other hand, cognitive impairment in CBD, once thought to be a rare or late feature, is indeed common and may present early in the course of the disease, sometimes before the onset of motor symptoms (Graham, Bak & Hodges, 2003; Vidailhet & Cochen, 2006; Kelley, Haidar & Boeve, 2009; Lee, Rabinovici & Mayo, 2011). With respect to episodic memory, an increasing number of studies show altered performances in CBD patients (Wenning, Litvan & Jankovic, 1998; Mathuranath et al, 2000; Cordato et al, 2001; Graham et al, 2003; Beck, Rohrer & Campbell, 2008; Le Ber,

Camuzat & Hannequin, 2008; Matuszewski et al, 2009; Kertesz & McMonagle, 2010a; Lee et al, 2011).

Apart from impaired executive test scores, our patient seemed unable to drive. We did not test him for driving abilities, but according to his wife's description, we inferred it had to do with his attentional and executive dysfunction, for instance difficulties to manage dual tasks, slowness of information processing, planning and using strategies to reach the end point. Executive functions seem to follow the same pattern of decline as episodic memory along with SD or CBD progression and severity (Graham et al, 2003; Kelley et al, 2009; Matuszewski et al, 2009; Rohrer, Geser & Zhou, 2010; Lee et al, 2011). These results point to frontal lobe dysfunction, including not only SD, but also CBD in the FTLD spectrum (Pillon, Blin & Vidailhet, 1995; Matuszewski et al, 2009; Kertesz et al, 2010a). Consistent with these findings is the known association of CBD with the other two clinical FTLD syndromes, progressive nonfluent aphasia and behavioural variant of frontotemporal dementia (Kertesz et al, 2007; Murray, Neumann & Forman, 2007; Rabinovici & Miller, 2010; Kouri, Whitwell & Josephs, 2011a). Frontal behavioural manifestations are present in four of the reported SD-CBD cases (Ikeda et al, 1996; Maturanath et al, 2000; McMonagle et al, 2006; Raggi et al, 2007), while abnormal performances on executive testing are reported in the fifth one (Luzzi et al, 2012) .

Our patient's language was marked by confrontation naming deficits, corroborated by the very low BNT score and by our locally developed naming test. Moreover, his pattern of performance has been reported in a similar patient with SD and CBS (Luzzi et al, 2012). His score (25/40, 62%) was identical to our patient's on a locally developed picture naming test, and remained stable two years later (24/40). Our patient's evolution, though, was not as favourable as evidenced by his poor results on the subsequent naming tests. Besides, progression of CBD pathology could explain the patient's striking change within a few

months, from the initial semantic to the later nonfluent form. An apraxia of speech, secondary to disorders of motor command, may contribute to the clinical picture (Hu, Parisi & Knopman, 2007; Williams et al, 2009; Kouri et al, 2011a). Apart from reduced fluency, though, our patient did not manifest the other characteristics of a typical apraxia of speech (Ogar, Slama, & Dronkers, 2005; Haley, Jacks, & de Riesthal, 2012). Additionally, the natural evolution of verbal output in SD is frequently reported to be nonfluent, leading up to mere mutism (Hodges et al, 2007; Kertesz, Jesso & Harciarek, 2010b; Harciarek et al, 2011). Unfortunately, many reports lack detailed characterization of the language abnormalities (Graham et al, 2003).

Our patient, though initially oriented, was nevertheless reported to have trouble finding his way in a familiar environment. This apparent discrepancy may not be as surprising as it seems. Spatial orientation is a generic term which encompasses several cognitive fields, i.e. spatial memory, semantic memory, visuospatial and executive processes. Spatial memory as the ability to recognize a particular landmark, place it in space and describe a route from one place to another, is generally preserved in SD (Pengas, Patterson, & Arnold, 2010; Mazzei, Brugnolo, & Dessi, 2010). This factor may contribute to the similitude of the MMSE orientation scores between SD and AD groups (Shimizu, Komori, & Fukuhara, 2011). However, impaired access to semantic memory in SD and AD, which prevents patients from identifying places and buildings, and from keeping a mental geographic representation thereof, is involved in spatial disorientation (Mazzei et al, 2010; Bessi et al, 2010). Furthermore, right-sided temporal atrophy, in atypical cases of SD or due to spreading of the disease over time, has been implicated in navigation problems and the “symptom of getting lost” (Thompson et al, 2003; Chan et al, 2009). Finally, way-finding strategies require intact executive functions which, if impaired, may cause spatial disorientation and “getting lost behaviour” in SD and AD patients (Chiu, Algase, & Liang, 2005; Pengas et al, 2010). Executive and visuospatial dysfunction may also be responsible for the disorientation,

without further specification, pointed out in some studies about CBD patients (Litvan, Grimes, & Lang, 1999; Grimes, Lang, & Bergeron, 1999).

Calculation impairment is part of several neurodegenerative disorders (Halpern, McMillan, & Moore, 2003). Growing evidence suggests a progressive degradation in SD patients' conceptual understanding of arithmetic, increasing as a function of disease severity (Cappelletti, Kopelman, & Morton, 2005; Julien et al, 2008). Procedures, i.e. the sequence of steps necessary for performing a calculation, show a gradual breakdown, a pattern we observed in our patient. Compensatory strategies become less efficient. With semantic decline, plausible errors decrease and implausible errors become more prevalent (Julien et al, 2008). A recent study provides evidence for an impairment of arithmetic knowledge even in patients with early-stage mild SD, supporting the notion that calculation cannot be considered an independent domain of the semantic system (Luzzi, Cafazzo, & Silvestrini, 2013). Besides, dyscalculia is frequently reported in CBD patients and may be correlated to CBD parietal cortex involvement (Mayer, Reicherts, & Deloche, 2003; Graham et al, 2003; Halpern et al, 2003; Halpern, Clark, & Moore, 2004; Halpern, Clark, & Moore, 2007; Troiani, Clark, & Grossman, 2011; Mathew et al, 2012).

CBD may initially present either as a cognitive or motor disorder (McMonagle et al, 2006). In our patient, parkinsonism emerged fairly late, altogether an unconventional evolution in the context of SD and a significant indicator of the underlying pathology. Motor disturbances initially presented as Richardson's syndrome with postural instability, recurrent falls, vertical gaze palsy, staring gaze, axial rigidity, bradykinesia and frontal dysexecutive syndrome (for criteria, see Litvan, Agid & Calne, 1996; Williams & Lees, 2009). They evolved into a CBS picture of asymmetric rigidity of the right limbs, the right upper extremity held in a fixed dystonic posture, neck dystonia and global apraxia. There was no evidence of the alien limb phenomenon, cortical sensory loss, or myoclonus, all possible features of CBS (for criteria,

see Mathew et al, 2012). Actually, overlapping presentations of PSP and CBS are frequent and may represent a diagnostic challenge (Kouri, Murray & Hassan, 2011b; Boeve, 2011; Kouri et al, 2011a). Even an atypical case of Alzheimer's disease is to be considered given the clinical picture, but this hypothesis was invalidated by the neuropathological findings (absence of senile plaques, absence of amyloid deposits, absence of 3R-tau isoforms in the neurofibrillary tangles) (von Gunten, Bouras & Kövari, 2006; Duyckaerts, Delatour & Potier, 2009).

With respect to neuroimaging, FTLD literature appears heterogeneous. Characteristic patterns of atrophy in the case of SD include asymmetrical temporal lobe, hippocampus and amygdala involvement, which spread over time to contralateral homologous areas and the frontal lobes (Rohrer JD, 2012). CBS presents with asymmetrical atrophy of frontal and parietal lobes, cerebral peduncles, midbrain tegmentum and corpus callosum (Koyama, Yagishita, & Nakata, 2007). Increased signal intensity is noted in frontal or parietal subcortical white matter (ibid.). Accordingly to current recommendations, structural imaging is used to distinguish the sub-types of FTLD and to differentiate CBS from PSP (Sorbi, Hort, & Erkinjuntti, 2012). Our patient's MRIs have been visually assessed by two senior radiologists. The second MRI showed the majority of the features of both diseases, SD and CBS, presumably an effect of the diseases progression and long duration. The first MRI was more specific of SD, showing asymmetrical temporal poles atrophy with left predominance.

At autopsy, our patient showed an extensive cortical atrophy. Neuropathological criteria of CBD comprise cortical degeneration in a peri-rolandic distribution, though atypical presentations are not uncommon, including the frontal lobe, peri-sylvian region and medial temporal lobe (Dickson et al, 2002; Wakabayashi & Takahashi, 2004; Murray et al, 2007; Kouri et al, 2011b; Dickson, Kouri & Murray, 2011). Atypical cases of PSP with severe cortical involvement have also been reported in which atrophy of frontal, temporal or parietal

lobes has been observed (Wakabayashi et al, 2004; Dickson, Ahmed & Algom, 2010). Our patient's predominant temporal atrophy fits neither CBD, nor PSP. Microscopic features enables further distinction : CBD is characterized by greater cortical tau pathology, greater threads accumulation in white matter than PSP, and by the presence of astrocytic plaques which are considered the most specific histopathological feature of CBD (Forman, Zhukareva & Bergeron, 2002; Dickson et al, 2002; Wakabayashi et al, 2004; Williams et al, 2009; Dickson et al, 2011). Ballooned neurons are not distinctive and their absence or rarity does not preclude the diagnosis of CBD (Dickson et al, 2002, Wakabayashi et al, 2004). 4R-tau-positive Pick body-like inclusions have already been associated with several conditions, including CBD and PSP (Ikeda, Akiyama & Arai, 2002; Armstrong et al, 2000; Miki, Mori & Hori, 2009; Kovacs & Budka, 2010; Kovacs, Rozemuller & van Swieten, 2012). In our case, the main neuropathological features consistent with CBD are the considerable cortical and subcortical involvement, the numerous astrocytic plaques and the extensive tau-immunoreactive cell processes in both gray matter and white matter (Armstrong, Cairns, & Lantos, 2000; Dickson et al, 2002; Forman et al, 2002; Murray et al, 2007; Kouri et al, 2011b). The inconstant argyrophilic properties of the 4R-tau lesions, an unusual finding in both PSP and CBD, could be linked to the "maturation" theory which parallels glial tau immunoreactivity and Gallyas staining pattern with maturation of the lesions, analogously to the concept of pretangles (Gallyas negative) and tangles (Gallyas positive) (Uchihara, 2007; Kovacs, Molnar & Laszlo, 2011). Silver-stained or not, an evolution of glial tau inclusions seems plausible and is substantiated by our original observation of protoplasmic reactive astrocytes with isolated perinuclear tau deposits. However, further evidence is needed to confirm these assumptions. Similar cases of atypical tauopathies have been described, including cases with massive subcortical tau accumulation and argyrophilic coiled bodies (Ohara, Tsuyuzaki & Oide, 2002; Tan, Piao & Kakita, 2005; Sakai, Piao & Kikugawa, 2006;

Giaccone, Marcon & Mangieri, 2008). Along with most of the authors, we consider our case as either an atypical form of CBD or a new variant of sporadic tauopathy.

In conclusion, our case supports and extends previous research in the FTLD spectrum. It also suggests that SD may not be a nosological entity as homogeneous as previously acknowledged. Several potential factors may contribute to explain this variability. 1) Historically, the notion of FTLD is recent and still evolving. The clinical syndromes undergo regular updating, making old definitions rapidly obsolete. In the future, non-semantic impairment in SD may prove more common than previously thought. 2) The relative rarity of SD in the examined population may have concealed some of its more subtle cognitive features. Differences in the neuropsychological testing could also be involved in them being passed over or trivialized. 3) As each FTLD phenotype may be underpinned by different neuropathological diseases, a certain degree of variety is expected in the clinical expression thereof. The topography of the brain lesions may even prove more important to clinical picture than the type of protein deposits. 4) In such a moving domain as FTLD, co-occurrence or a sequence of several clinical syndromes is probably the rule rather than the exception. We intended here to disentangle the respective contribution of the diverse clinical syndromes and neuropathological data. The association of SD as initial presentation, later CBS evolution and CBD-like 4R tauopathy is most unusual. To our knowledge, this is the first published case of SD associated with CBS with full-blown cognitive and motor symptoms, and neuropathological data. This atypical case stands as an example of FTLD overlapping syndromes and stresses the need for further studies to understand the pathological pathways of neurodegenerative disorders.

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Table 1. Neuropsychological examinations

		T0 (initial)	T+7 months	T+16 months	T+25 months
Global	MMSE[1]	**23/30**			
Orientation	Time, place, self	3/3	3/3	3/3	**1/3**
Language	Boston Naming Test[2] A	**13/34**			
	Boston Naming Test D			**6/20**	
	Naming of line-drawings[3]	**22/36**	**20/36**	**4/6**	
	Naming or pointing real objects				**0/7**
	Regular, irregular and non words[3]				
	Repetition	17/17		12/12	+
	Reading	**21/24**	**21/24**	++	++
	Writing	**14/15**	**9/15**	**3/11**	
	Comprehension	+	+	++	+++
Calculation		+		++	
Constructional and ideomotor praxis	Clock drawing test[4]	**5/7**			
	Pantomime[5]	-	-	-	
	Symbolic gestures[6]	-	-	-	
	Imitation of meaningless gestures[6]	+	+	+	
	Copy of geometric figures[7]	-	-	-	
	Buccofacial gestures[6]				+++
Visuoperceptive skills	Poppelreuter-Ghent's overlapping figures test[8]	-	-	++	+++
	Kanizsa's illusory contours[9]	-	-	-	
	Birmingham Object Recognition Battery[10]				
	Size match task		28/30		
	Orientation match task		25/30		
	Line bisection task[11]			-	
Memory	Hebb digit span forwards [12]	6		5	5
	Buschke selective reminding test (16 items)[13]				
	Immediate recall	**4/16**			
	Delayed free recall	**1/16**			
	Delayed cued recall	**1/16**			
	Baddeley's Shapes Test[14]				
	Total	**9/75**			
	Immediate recognition	**4/30**			
	Delayed recall	**0/15**			
	Baddeley's Doors Test[14] A	**4/12**		**3/12**	
	Semantic memory[3]				
	Verbal				
	Auditory input	++	++	+++	+++
	Visual input	++	++	++	+++
	Tactile input	+			
	Non-verbal				
	Famous people	**2/7**			
	Famous buildings	**2/6**			
Executive functions	Verbal fluency[7](2 minutes)				
	Semantic (animals)	**7**			
	Phonemic (p)	12			
	Luria's graphic sequence test[15]	5	5	5	
	Trail Making Test[16]A	67"	**120"**	**178"**	
	Trail Making Test B	**196"**	**336"**	**240"**	
	Regard's Five-Point Test[17]	**11**			
Others	Activities of Daily Living [18]	6/6		**4/6**	**0/6**
	Instrumental Activities of Daily Living[19]	8/8		**3/8**	**0/8**

Bold numbers = abnormal scoring

- no impairment, + mild impairment, ++ moderate impairment, +++ severe impairment

[1]Folstein, Folstein & McHugh, 1975 [2]Kaplan, Goodglass & Weintraub, 1983; Thuillard Colombo & Assal, 1992 [3]locally developed semantic battery (see text) [4]Shulman, Shedletsky & Silver, 1986 [5]Duffy & Duffy, 1981 [6]Rothi, Ochipa & Heilman, 1991 [7]Morris, Heyman & Mohs, 1989 [8]De Renzi, Scotti & Spinnler, 1969 [9]Kanizsa, 1976 [10]Riddoch & Humphrey, 1993 [11]Albert, 1971 [12]Hebb, 1961 [13]Grober & Buschke, 1987 [14]Baddeley, Emslie & Nimmo-Smith, 1994 [15]Luria, 1966 [16]Army Individual Test Battery, 1944 [17]Regard, Strauss & Knapp, 1982 [18]Katz, Ford & Moskowitz, 1963 [19]Lawton & Brody, 1969

Table 2. Semantic battery tests

	% identifiable drawings (copy & memory)		% naming errors		% picture pointing errors		Number of errors about probe questions	
Assessment	T0	T+6 months	T0	T+6 months	T0	T+6 months	T0	T+6 months
Furniture	100	100	16	16	0		0	
Tools	100	50	0	16	0		1	
Clothes	100	33	16	16	0		0	
Animals	18	0	66	33	33	50	1	
Fruit	83	0	33	83	16	0	1	
Vegetables	50	0	66	100	33	66	4	

Table 3. Semi-quantitative assessment of histopathological findings (adapted from Dickson et al, 2002)

	Neuronal loss and gliosis	Tau-positive neurons	Tau-positive glia
Cerebral cortex			
Frontal	++	+++	+++
Temporal	+++	+++	+++
Parietal	+	+++	+++
Occipital	+	+	+
Subcortical areas			
Hippocampus	+++	+++	+++
Amygdala	++	+++	+++
Nucleus of Meynert	+	+++	+++
Caudate & putamen	+	+++	+++
Globus pallidus	+	+++	+++
Thalamus	+	+++	+++
Subthalamic nucleus	+	+++	+++
Brainstem	++	+++	+++
Cerebellum	+	++	++

0 = none, + = mild, ++ = moderate, +++ = severe

Table 4. Summary of reports of fluent aphasia in CBD/CBS patients

Source	Cases with fluent aphasia (n)	Authors' characterization of the aphasia	Authors' characterization of the motor symptoms	Neuropathological diagnosis
Ikeda et al (1996)	1	Primary progressive sensory aphasia	Muscle rigidity, nuchal dystonia, small-stepped gait, neck rigidity, neck bent posteriorly, muscle rigidity of the limbs	CBD
Mathuranath et al (2000)	1	Progressive fluent aphasia	No motor symptoms	CBD
McMonagle et al (2006)	1	Fluent receptive Wernicke's aphasia (later renamed SD)	CBD syndrome	CBD
Raggi et al (2007)	1	SD	No motor symptoms	Not available
Luzzi et al (2012)	1	SD	CBS	Not available

Figure 1. Drawing by memory (elephant)

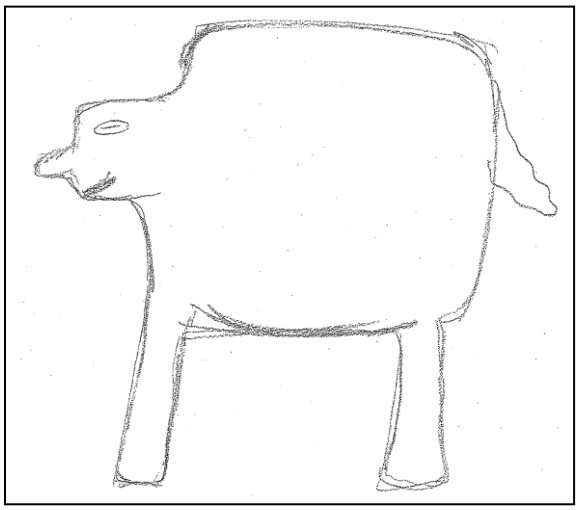


Figure 2. Copy of line-drawing

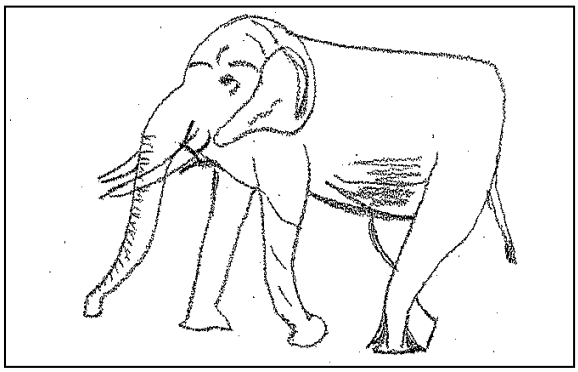
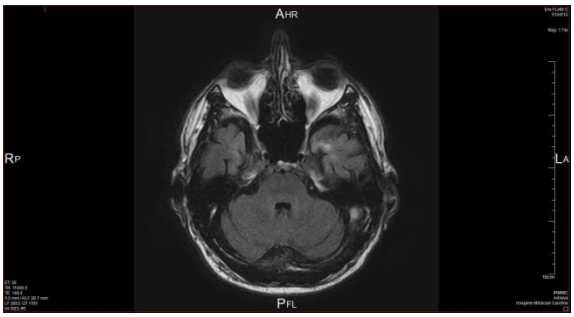


Figure 3. First MRI (T0, initial diagnosis). FLAIR (a) and T1-weighted (b) images, showing predominant atrophy of the left temporal pole.

a



b

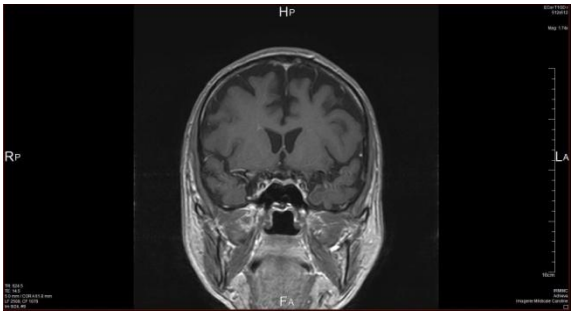
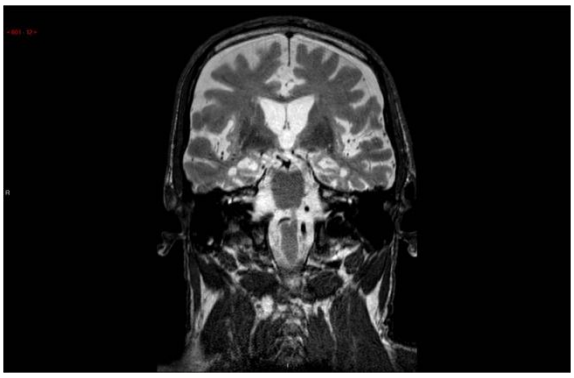


Figure 4. Second MRI (T+ 25 months). T2 (a) and T1 (b) weighted images, showing severe atrophy of temporal lobes and hippocampus.

a



b

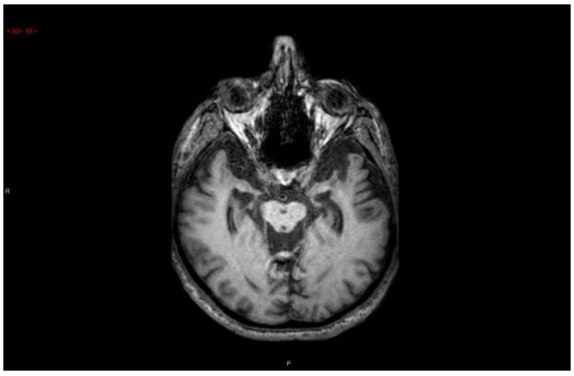


Figure 5. Neuropathological findings

a-f: Tau immunostaining of neuronal and glial inclusions (anti-phosphorylated tau antibody): astrocytic plaques (a), protoplasmic reactive astrocytes (b), oligodendroglial coiled bodies (c), achromatic ballooned neurons (d), intraneuronal inclusions in the granule layer of the dentate gyrus of the hippocampus (e). Tau inclusions are positive for tau 4R (f). Original magnification: x600 for a, b, d, x400 for c, f, x200 for e.