Beyond behavioral changes in semantic dementia: principal hurdles on the road to the clinic

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Abstract: The neurology, psychiatry and psychology areas have played a fundamental role in the characterization of cognitive disturbances associated to dementia disorders, which has contributed to the improvement of diagnostic and therapeutic procedures. Semantic dementia is a subgenre of frontotemporal dementia, consists in a syndrome of primary progressive aphasia characterized by the loss of semantic knowledge, with the preservation of other cognitive functions, such as visual memory, visuospatial capacity, and executive abilities. Thus, the relevance of this study consists in thoroughly analyzing the main alterations in which concerns the behavior of semantic dementia, aiming to know more about this rare subtype of frontotemporal dementia, so that in the future its clinical manifestations, diagnosis and treatment are better elucidated. A narrative literature review was executed in the Medline database (PubMed), from 2010 to 2022, about behavioral alterations in semantic dementia. The present literature review article demonstrates the current comprehension about cognitive, behavioral, and functional alterations as a semantic dementia consequence, besides providing relevant information to prioritize the therapeutic offered to patients that have such a condition. Furthermore, more studies addressing this subject are paramount since the existing studies are still not sufficient to completely elucidate the behavioral changes in semantic dementia.

Keywords: Dementia; Semantic dementia; Behavioral changes.

1. Introduction

The areas of neurology, psychiatry, and psychology have played a crucial role in characterizing cognitive disturbances associated with dementia disorders. This has contributed to improving diagnostic and therapeutic procedures, especially through the identification of cognitive changes that occur in the prodromal phase of the disease and

tracking clinical progression [1]. Frontotemporal dementia (FTD) is a neurodegenerative disease characterized by progressive behavior disorders that can be accompanied by deficiency in the language process and neuronal deterioration, notably in the frontal and temporal lobes [2].

Semantic dementia (SD) is a subtype of frontotemporal dementia characterized by a primary progressive aphasia syndrome with the loss of semantic knowledge and the preservation of other cognitive functions, such as visual memory, visuospatial capacity, and executive abilities [1]. Epidemiologic studies estimate FTD prevalence at approximately 11/100,000 individuals, with SD cases representing approximately one-third of the cases [3]. The term "*Semantic dementia*" (SD) was first described in 1904 by Arnold Pick and properly named in 1989 by Elizabeth Warrington. Since then, it has been used to define linguistic agnosia classified in frontotemporal dementia syndromes [4].

Although considered a rare incidence, SD is one of the most likely dementia manifestations in the presenile age group, representing on average 10-15% of frontotemporal dementia cases [5]. Its occurrence is strongly related to the genetic factor, with most sporadic mutations, but approximately 20% of cases are linked to autosomal dominant inheritance of various genes, such as chromosome 9 open reading frame 72 (C9orf72), progranulin (GRN), and microtubule-associated protein tau (MAPT) [1, 6] (Table 01). Concerning pathophysiology, protein deposition, such as microtubule-associated protein tau, transactive response DNA-binding protein of 43 kDa, and sarcoma-associated fusion proteins, have an essential role in the neurodegeneration process, leading to cerebral microangiopathy, neuronal loss, and bilateral and asymmetrical atrophy of the temporal lobe, especially in the middle temporal and inferior gyri [1, 7].

When evaluating the clinical condition of a patient with semantic dementia, a significant alteration in comprehension and naming isolated words associated with associative agnosia is noticeable, despite the preservation of speech comprehension cognitive functions in its syntactic and grammatical aspects, as well as autobiographical and episodic memory [8, 9]. Diagnosis of SD is primarily based on a detailed anamnesis correlated with neuropsychological tests [10, 11] and laboratory and neuroimaging tests, such as magnetic resonance imaging [MRI] [11]. However, difficulties identifying alterations in the earlier stages of the disease, as well as the absence of specific biomarkers for the disease, can present challenges in the diagnosis of this condition. This highlights the importance of clinical investigation for early diagnosis [6].

Thus, the relevance of this study is to thoroughly analyze the main alterations concerning the behavior of semantic dementia. This aims to increase knowledge about this rare subtype of frontotemporal dementia, so that its clinical manifestations, diagnosis, and treatment can be better elucidated for recognition by health professionals in the future.

2. Clinical presentation and cognitive profile

Frontotemporal Dementia (FTD) is a neurodegenerative disease with early onset and varied clinical presentations. It can be understood as a primary progressive aphasia syndrome with dysfunction of normal behavior [12]. Verbal fluency is a sensible tool used to measure linguistic capacity, semantic memory, and executive functioning. However, qualitative changes in verbal fluency of FTD patients are currently underestimated [13]. FTD is the fourth most prevalent form of dementia presentation, surpassed only by Alzheimer's disease, vascular dementia, and dementia with Lewy bodies [4]. When addressing the causes of early onset dementia, it is second only to Alzheimer's disease. Additionally, FTD can be divided into three subtypes: SD, behavioral variant FTD, and progressive non-fluent aphasia, with estimated prevalences of 20%, 60%, and 20%, respectively [4].

SD is a subtype of Frontotemporal Dementia (FTD) characterized by progressive aphasia caused by the loss of verbal and non-verbal semantic memory, with the initial preservation of other cognitive abilities [14] (Table 01), and severe local atrophy in the

temporal lobe [9]. SD can also be considered a semantic variant of primary progressive aphasia [4]. It can be characterized by three evolutionary stages: 1) early-stage, when the first symptoms appear, mainly constant searching for words and names when trying to express themselves (disorder generally associated with left hemisphere lesions); 2) middle-stage, after about three years since the pathology's installation, evolves to difficulty in understanding other people, especially names and known faces or famous people (characteristics generally associated with right hemisphere lesion). Surface dyslexia and dysgraphia can appear in this period; 3) late-stage, after six to eight years of the disease's evolution, in which the patient begins to present severe damage in communication abilities, as well as important modifications in behavioral habits, such as weight problems, lethargy, and incapacity to recognize people by their faces. In this last stage, the patient progresses to death [4].

Furthermore, there is a relation of resemblance in the symptomatology presentation between SD and autism spectrum disorder (ASD), with about 75% of SD patients scoring above the cut-off value for ASD diagnosis in the short version of the PARS test (Pervasive Developmental Disorders Autism Society Japan Rating Scale), and the presence of these traits is associated with the duration of the disease and cognitive decline [9].

Initially, SD presents a reduction in the comprehension of simple words with a single structure, while preserving good understanding of more complex words. The clinical presentation of the Semantic Dementia patient is characterized by a significant alteration in the comprehension and naming of isolated words, along with associative agnosia. Additionally, there is preservation of cognitive functions used to comprehend speech, with adequate grammar and syntax, as well as autobiographical and episodic memory [9]. The hypothesis that lesions in the anterior region of the temporal lobe favor the characteristic of damaged semantic generalization was considered, which would make it difficult to visualize the whole context associated with language during a conversation [15]. When performing the PARS test on SD patients, it was found that only 80% interpreted language in the literal sense, 75% had difficulty comprehending what was said in each situation, and 75% had difficulty understanding feelings and other people's thoughts [9]. Furthermore, other verbal manifestations that can be present in SD patients are loss of semantic memory in the verbal domain, difficulty reading (surface dyslexia) and writing (dysgraphia), difficulty finding the right word (anomia), and a tendency to express themselves vaguely [4].

Although attention has been focused on the verbal deficiencies in SD, the behavioral symptoms, which are included in the consensus criteria of SD as supportive characteristics, are also clinically important. They found that some behavioral symptoms, including selfishness, more selective dietary patterns, repeated themes, and adhesion to daily routines, were more frequent in SD [9]. A prevalence of 91% for selfishness in SD patients was identified. The lack of empathy was also attested, being more prevalent in SD than in behavioral variant frontotemporal dementia [16]. When addressing neuropsychiatric manifestations, it was noted that 33% of SD patients presented obsessive-compulsive behaviors, 44% had depression, 22% had anxiety, and 11% had agitation [17].

When establishing comparisons between SD and other pathologies that have dementia characteristics, such as Alzheimer's disease, it was possible to observe some discrepancies in some clinical manifestations that can be of great relevance to diagnose this spectrum of diseases accurately. For example, SD causes more socioemotional behavioral dysfunction, such as disinhibition, aberrant motor behavior, and eating disorders than other progressive dementias and Alzheimer's disease [18] (Table 01).

Selfishness, more selective dietary habits, repetitive themes, and adhesion to daily routines are more frequent in SD when compared to behavioral variant FTD [19]. Bozeat et al. compared SD, behavioral variant FTD, and Alzheimer's with their own questionnaire. Mental rigidity, loss in the relation of sympathy/empathy, and wake were more frequent in SD [20]. When comparing SD with Alzheimer's through the PARS test, there was an incremental advantage in favor of SD in four items: an unbalanced diet, under-

eating, selfishness/lack of empathy, difficulty understanding and interpreting other people's feelings, and only interpreting sentences in a literal way, presenting difficulty in understanding jokes [9] (Table 01).

3. Cognitive profile

Patients with SD still show relative preservation in visuospatial ability, decision making, and memory, particularly in visual memory [14]. Like Alzheimer's disease and other types of FTD, SD typically produces speech changes initially, while fluency, syntax, and phonology remain preserved [21]. In the DSM-IV, dementias are characterized by the deterioration of at least two cognitive functions, including memory and language changes, confusion, disorientation, intellectual compromise, and personality modification. These changes impact the patient's daily activities. Specifically, in SD, it is possible to find personality disorders, antisocial behavior, and disinhibition (which usually precedes cognitive decline). Additionally, in terms of language, the comprehension of isolated words is usually preserved, although difficulty in associating words and images is also evident [22]. Modest difficulty in understanding longer sentences [23] and deficits in executive functions such as planning, and inhibition [24] can also be observed.

Semantic memory is typically preserved [25], while repetition can be enhanced [echolalia] and writing can be hyperfunctional (hypergraphia) [26]. Episodic memory is often compromised in SD patients [27], and autobiographical memory is commonly affected at all stages of the patient's life, with no differences between these gaps, and confabulations may be observed [28]. Executive functions, such as planning/inhibition, problem-solving, and processing, are usually affected from the beginning of SD's onset [24]. Visuospatial disorientation may also be noticed when the disease reaches intermediate stages [29]. One of the main characteristics of SD is the preservation of syntax and articulation, with possible disturbances in word comprehension, severe anomia, and decreased performance in fluency tests. These deficits are usually attributed to the impairment of semantic memory [22].

4. Genetic Physiology of Semantic Dementia

Frontotemporal dementia (FTD) is a group of diseases almost exclusively within the spectrum of neurodegenerative diseases, and that have a highly hereditary character, with about 30% of the patients having a family history. As a result, FTD's heredity has been a relevant object of study, including the initial investigation through the patient's family history absence or presence. Score systems for FTD family history were developed, such as the Goldman score and the Penn score [5].

Most FTD genetic causes are inherited as autosomal dominant with variable penetrance, depending on which gene suffered a mutation [30]. Regarding gene mutation, the majority of FTD heredity is explained by mutations in 3 genes: Progranulin (GRN), Microtubule-associated protein Tau (MAPT), and Chromosome 9 open reading frame 72 (*C9orf72*) [31], with more rare mutations in other genes such as *CHMP2B, VCP, TBK1, TIA1, OPTN, TARDBP, CCNF,* and *CHCHD10* [6]. However, C9orf72 seems to be the most frequent cause of genetic FTD in the world, followed by GRN and, finally, MAPT [5].

Regarding Chromosome 9 open reading frame 72 (*C9orf72*), the most common cause of familial FTD comes from the repeat expansion of GGGGCC nucleotides in the non-coding region of the *C9orf72* gene. Besides, literature reports that the penetrance increases with age and exhibits anticipation. Clinically, patients most frequently present bvFTD, ALS, FTD/ALS, and less commonly nfvPPA, CBS, and svPPA. It was also observed that patients with mutations in C9orf72 present hallucinations and delusions more commonly. The second most prevalent mutant gene is Progranulin (*GNR*) located on chromosome 17. The GNR mutation exhibits incomplete penetrance and, probably, anticipation phenomena. The onset of symptoms varies between the age gaps of 30 and 80 years old. Clinically, patients present with bvFTD and, less commonly, nfvPPA,

svPPA, CBS, Parkinson's disease, and Alzheimer's disease. Visual hallucinations and psychosis were also related to patients with this mutation [30]. Furthermore, Microtubule-associated protein Tau (*MAPT*) is a gene located on chromosome 17. The mutations in this DNA fragment have high penetrance, being rare in patients without a family history of dementia, parkinsonism, and other neurological conditions. Symptoms and similar presentations to schizophrenia have already been related. Clinically, the presentation with the same gene is variable even in the patient's same family and can include bvFTD, svPPA, nfvPPA, PSPS, CBS, or amnesia presentations such as Alzheimer's disease [30].

In Primary Progressive Aphasia (*PPA*), a neurodegenerative syndrome associated with Frontotemporal Dementia, language impairment is the most preponderant clinical characteristic, appearing during the early stages of the disease while other cognitive and behavioral domains are relatively preserved. The most common gene variants that cause FTD, besides MAPT, GRN, and C9orf72, are PSEN1 [32]. It is worth mentioning that a central clinical and pathological phenotype is recognized for each gene, although the clinical distinction is still not sufficiently defined. Thus, no clear and definite correlation of the genotype-phenotype has been identified until the present moment [33].

Regarding the patient's age at symptom onset, the starting age of symptoms in FTD varies with the interaction of recently identified genetic modifiers, including *TMEM106B*, particularly in *GRN* carriers, and a polymorphism in a locus containing two superimposed genes, *LOC101929163* and *C6orf10*, in *C9orf72* carriers. In *GRN* and *C9orf72* carriers, *TMEM106B* was identified as a genetic modifier, with the strongest association found in *GRN* carriers than in C9orf72 carriers. A lower starting age in *GRN* carriers can be related to the carrier of a risk allele, with homozygous carriers of the protective allele rarely found in symptomatic carriers of *GRN*, suggesting that this can be an age-related penetrance factor. The other risk modifier recently identified in *GRN* carriers, *GFRA2*, does not seem to affect the starting age of the disease. However, a *C9orf72* study in the carriers identified two superimposed genes (*LOC101929163* and *C6orf10*) in chromosome 6 that were related to the starting age [5].

Although some studies on the starting age and the type of mutant gene exist, the genetic contribution to FTD's clinical phenotype, including starting age, symptoms, and disease progression, is not totally clear [31]. More studies on the genetic participation in this disease are necessary to enlighten still incomplete information. Therefore, the creation of more genetic tests in pre-symptomatic patients is already being observed. However, this has not yet been reflected in the development of a specific test protocol for FTD or in the delivery of appropriate psychological support mechanisms for those who live in the risk phase [5].

5. Behavioral changes

SD is a group of neurodegenerative disorders that primarily and progressively affect language expression and comprehension [34] (Table 01). It is a disease that has an expressive impact on the social behavior of affected patients, leading to sudden personality changes that directly affect interpersonal relationships. Generally, it manifests as a gradual deterioration of emotional control and expression, the ability to manage critical decision-making analysis, and the loss of cognitive functions [10].

As previously mentioned, SD is a neurodegenerative disease with early onset and various clinical presentations. Diagnosis is often delayed as it can be mistaken for psychiatric manifestations due to the similarity of behavior presented in these dysfunctions, such as bipolar disorder, schizophrenia, obsessive-compulsive disorder (OCD), and autism spectrum disorder [6]. These disorders also lead to limitations in social management and have a greater prevalence in the world population. Therefore, correct investigation is necessary to initiate the most adequate therapy aiming to increase the manifestation of behavioral symptoms [35], as mentioned later in this study.

When evaluating the clinical presentation of an SD patient, there is an expressive symptomatic manifestation through behavioral alterations that are repeated among ob-

served patients. Frequently, patients behave in a stiff and inflexible way [36] (Table 01). Among the clinical findings, progressive loss of language performance is often highlighted due to its higher prevalence. This is known as anomy, a disorder that promotes a notable limit in the patient's social relationships since progressive semantic memory loss leads to significant limitations in verbal communication [14].

In addition, neuropsychiatric alterations are highlighted, such as an obsession with specific themes associated with stereotyped behaviors [e.g., compulsion for games or losing weight], changes in dietary habits (episodes of polyphagia, dysregulation of satiety perception, craving for uncommon culinary combinations, or even inanimate objects), loss of manners at the table [37], as well as loss of empathy, apathy, demonstration of indifference to other people's feelings or situations, exhibitionism, and selfishness [36, 38, 39].

6. Diagnosis and treatment

Anatomically, SD affects the anterior region of the temporal lobe in both hemispheres. Correlations between gray matter in the anterior temporal lobe and the association of object names with images, as well as naming of pictures, have shown signs of hypometabolism in the cortical region, and diagnosis was made possible through the use of neuroimaging [19]. Additionally, MRI scans have shown that the left temporal pole is more atrophic in the early stages of the disease, and as the pathology progresses, atrophy supervenes in the right temporal pole and in other areas connected to the left temporal pole [20].

Clinically, SD patients typically present with a reduction in comprehension of simple words, while preserving good understanding of more complex words, as well as relative preservation of visuospatial capacity, decision making, and memory, particularly visual memory. However, diagnosing SD patients can be challenging, as there is no gold standard test or defined methodology for comparing results [34], and the lack of such a test can lead to failure to recognize language impairment in initial clinical conversations [40]. In rarer cases, patients may experience incapacity to recognize objects [visual agnosia] or even family members [prosopagnosia] through vision [15]. Thus, a diagnosis of SD is suggested by the presentation of certain conditions in the patient, such as anomy, unfamiliarity with simple words, and lack of recognition of names for common objects [34].

Therefore, when looking to diagnose a patient with SD, a thorough anamnesis, attentive physical examination, and complementary exams such as neuropsychological tests, brain MRI, and analysis of cerebrospinal fluid are necessary. Formal cognitive tests, such as the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MOCA), Cognitive Examination, tests of object recognition, and the Cambridge Neuropsychological Test Automated Battery (CANTAB) language test, should be executed to evaluate cognitive deficits [4]. In these cases, neuropsychological tests can be used to evaluate patients' comprehension of both concrete and abstract verbs [2].

Besides the tests mentioned above, a specific language test for patients suspected of having SD is also utilized, named the Concrete and Abstract Word Synonym test or the Pyramids and Palm Trees test, which is a non-verbal test of semantic memory [4]. The Concrete and Abstract Word Synonym test consists of 25 target words, with some having high concrete classification and others with decreased concrete classification, paired with a synonym that appears more frequently and one distractor item of similar frequency [1]. However, in the Pyramids and Palm Trees test, the patient must choose between two alternatives, such as a palm tree and a pine, which is closer to the presented object, a pyramid. The test is executed first in a non-verbal way through images and then in a verbal way [11].

In this context, before presenting the signs and symptoms, it is highlighted that while the pharmacologic and nonpharmacologic treatment of symptoms in the most common type of dementia, such as Alzheimer's disease, is well described in clinical practice, the SD pharmacologic treatment is only discussed secondarily [4]. Therefore,

currently, there is no pharmacologic intervention to cure or minimize the SD effects [41]. Furthermore, there are no modifying treatments to fight against the development of SD, and the evidence of the efficiency of symptomatic treatments is scarce [15]. In that sense, research indicates that nonpharmacologic interventions in individuals with SD can help them re-learn lost vocabulary and benefit from other types of behavioral therapies. Thus, therapy in SD cases should focus on maintaining or enhancing access to names and semantic representations [41].

Many studies suggest that therapies for word retrieval, such as semantic, phonological, and orthographic interventions, lead to substantial benefits in the naming abilities of SD patients and have a generalized effect on functional communication [42]. Therefore, lexical retrieval treatment is the most common type of intervention performed in SD patients to treat progressive difficulty in finding words. Generally, the test uses a hierarchy of activities projected to promote strategic recruitment of semantics, orthography, and phonology to enhance word retrieval and stimulate autosuggestion, improving naming capacity, spoken content, and the efficiency of spontaneous speech, ultimately promoting improvement in naming abilities in the patient's routine [15].

One type of therapy used is Semantic Feature Analysis (SFA), which aims to activate the semantic network of the patient by providing a structured idea. SFA consists of a semantic characteristic of a target item, such as a hammer, along with its properties and characteristics. If the patient has difficulty naming the object or image of the hammer, they are signaled with "semantic characteristics." Recent studies suggest that successful execution of SFA therapy can improve the patient's lexical retrieval for up to 12 months [16]. Evidence suggests that 20 to 60 minutes of daily training is effective in producing short-term benefits, although some individuals have shown benefits in less time [14].

In addition to the therapeutic measures mentioned above, non-invasive brain stimulation and neuromodulation can provide a promising therapeutic strategy. Two of the most common technologies used in non-invasive brain stimulation are repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tCDS). rTMS stimulates intracranial electric current that modulates neuronal activity, while tCDS generates a polarization gradient in a cortical area between the electrodes, modulating cortical excitability in its limits. These therapy techniques assume that weak electric currents can interact with neuronal networks that correspond to language areas and promote neuronal plasticity, allowing short-term modulations and eventually clinical recovery [43].

Therefore, the management of SD patients should include a range of therapeutic options, including retrieving and compensatory strategies, educational and support groups, and care for partners and family members. These therapeutic options have the potential to become more accessible due to advances in telemedicine, which can overcome geographic barriers and offer medical care with similar efficiency as in-person therapy [41]. Patients with typical SD conditions, such as anomy or other types of cognitive decline, should be encouraged by their relatives to seek immediate medical attention to reach a clinical solution [4].

4. Conclusion

The present literature review article demonstrates the current comprehension about cognitive, behavioral, and functional alterations as a SD consequence, besides providing relevant information to prioritize the therapeutic offered to patients that have such a condition. Furthermore, more studies addressing this subject are paramount since the existing studies are still not sufficient to completely elucidate the behavioral changes in semantic dementia.

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