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New Insights into Frontotemporal Lobar Degeneration

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The three different subtypes of frontotemporal lobar degeneration (FTLD) by Neary criteria can be characterized as clinical syndromes, anatomically predominant case in one single category with possible different neuropathology. With advances in FTLD research, the concerns regarding the use of Neary Criteria for FTLD Research have emerged. The issues are lack of incorporation of different demographics, poor distinction from neuropathologic finding, un-operationalized diagnostic core item, and underevaluation of behavioral or emotional symptoms that is important in FTD manifestation. With the scientific forward in dementia research, including the imagings, a cross-culturally valid and scientifically ept new research criteria is prerequisite for study of FTLD and its related conditions.

Key Words: *Neary criteria; FTLD; Behavior; Demographics; Imaging*

In 1998 Neary and colleagues proposed new research criteria for frontotemporal lobar degeneration (FTLD)[1]. The Neary criteria (NC) outlined three clinical syndromes all subsumed under the category of FTLD. The three major FTLD subtypes were frontotemporal dementia (FTD), semantic dementia (SD) and progressive non-fluent aphasia (PNFA). FTD was defined as a progressive behavioral syndrome and core criteria included early loss of social conduct, early loss of personal conduct, emotional blunting and loss of insight. SD was defined as a progressive language disorder with loss of word meaning, semantic paraphasias and/or a progressive perceptual disorder with prosopagnosia or visual agnosia. The inclusion of a perceptual disorder under the heading of this language syndrome acknowledged the presence of a predominantly right temporal lobe disorder associated with SD. PNFA was characterized by non-fluent spontaneous speech with at least one of the followings; agrammatism, phonemic paraphasias and anomia.

It has been almost seven years since the NC were first published and there are now numerous papers that have used the NC to describe patient populations suffering from FTLD. These studies facilitate a better understanding of the epidemiological[2, 3], clinical and imaging features[4-8] and treatment responsiveness[9] of this group of patients. Additionally, evaluation of patients using FTLD nomenclature has led to new findings. For example, the NC did not suggest that the FTLD subtypes should differ with regards to age, sex, or pathology but there are new studies to suggest that there are important demographic distinctions between FTD, SD and PNFA[10]. There are still few studies with neuropathological confirmation in the FTLD subtypes other than for FTD but there are many new findings related to the histological features of FTLD[3, 10, 11]. In addition, studies have criticized certain aspects of the NC suggesting that the individual items are difficult to operationalize and that many patients with FTLD do not fulfill the core criteria[12]. Still others worry that patients with non-FTLD related disorders including AD will be improperly classified as FTLD using the loose definition of PNFA[13].

In this paper, we review the demographic features of FTD, SD and PNFA and suggest that the three subtypes of FTLD represent populations with somewhat different demographic features. Also, some of the concerns associated with the NC are discussed. Finally, we note the neuropathological correlates of FTLD.

Insights into asymmetric brain degeneration from SD

Beginning with the first descriptions of FTLD-related disorders, most investigators combined thought of the frontal and temporal variants of this condition as one disorder. Pick's original patients suffered from temporally predominant variants of FTLD (SD) and had prominent language abnormalities[14]. Only later did Pick describe frontally predominant cases. Ironically, despite Pick's emphasis on aphasia and semantic deficits associated with focal temporal lobe degeneration, until recently most studies on "Pick's disease" described patients with frontally predominant clinical and pathological syndromes[15, 16]. One great strength of the new FTLD criteria is that they capture left and right, frontal and temporally predominant cases in one single category.

Beginning with Pick's first patient there has been an over-representation of cases with asymmetric left brain pathology. In Sjogren's 1952 series, left-sided cases were more common to those with right-sided degeneration[17]. Similarly, when we looked at the number of left-sided versus right-sided SD cases evaluated at UCSF using neuroimaging to measure temporal lobe volumes, there was a nearly three to one ratio of left relative to right-sided temporal cases[16].

There are several potential explanations for the higher frequency of left-sided cases. One possibility is that patients with the symptom complex associated with the left-sided cases (predominantly language) are more likely to reach memory disorders clinics than are patients with right-sided disease where the clinical syndrome is predominantly behavioral. Recently, Seeley and colleagues have reported that right-temporal patients begin with emotional changes that make them hard to distinguish from patients with late-life depression [18]. Additionally, as right temporally predominant patients progress antisocial behavior, social isolation and resistance to physician visits and cognitive testing become common. These diagnostic factors might diminish the number of right-sided cases captured in research cohorts. Another potential explanation for the over-representation of left-sided cases in SD series is that some right temporal patients begin with behavior and might be classified as FTD rather than SD. This potential confound is less likely in the UCSF cohort because we defined cases anatomically.

A biologically-based explanation is that the left temporal lobe is selectively vulnerable to degeneration. Probing of brain asymmetry and selective left temporal vulnerability began with Norman Geschwind and is now being explored by Dan Geschwind. The left temporal lobe has a longer time for development *in-utero* making it more likely to be influenced by *in-utero* insults. Also, even though the planum temporale is larger on the left side, the left temporal lobe tends to be smaller than the right[19]. Does exaggeration of normal mechanisms associated with left temporal lobe development contribute to SD? In support of a developmental hypothesis for SD, Mesulam and colleagues have described several FTLD patients in whom a small middle cranial fossa was present, pointing to an early insult as a factor in the pathogenesis [20]. Only with larger population-based studies will it be possible to verify a left-sided predominance and begin to understand the asymmetry of this and other FTLD subtypes.

What are the demographic features of FTLD?

Publication of the NC has facilitated research into the prevalence, the relative distribution of clinical subtypes and the age and sex differences associated with FTLD and FTLD subtypes. In a multi-center five year study from neurological clinics at UCSF and UCLA and a psychiatrically based clinic at Munich, Germany, 353 consecutively studied patients were classified using the NC with regards to FTLD subtype frequency. Age and sex differences between the subtypes were reported. The groups showed remarkably similar prevalence for the three FTLD populations with FTD the most common subtype (60%) compared to PNFA (25%) and SD (19%) [10]. Not surprisingly, the psychiatric center saw more behavioral (FTD) than language cases (SD, PNFA), but even this difference did not reach statistical significance. FTLD was found to be an early-age-of-onset disorder with FTD the youngest (age 58), PNFA the oldest (age 63) and SD in between. Finally, both FTD and SD showed a male predominance of approximately two to one while PNFA had a slightly greater representation of females. Studies from Cambridge also suggest a higher prevalence for males with FTD although the sex difference for SD was approximately equal[3].

The male predominance for FTD and possibly SD offers potential insights into the etiology of these conditions. Frontal lobe development is slower in males than in females and throughout the lifetime females have slightly larger frontal lobes than do males when volumes are corrected for head size [21]. Similarly, females slightly outperform males on tasks of frontal function and have a much lower frequency of antisocial disorders[22]. Whether this normal difference between the two sexes with regards to frontal lobe vulnerability is a

factor in the male predominance of FTD is unknown. Another possible explanation is that males are more likely to be diagnosed with FTD than are females because they are more prone to behavioral disorders, while females are more prone to be diagnosed with PNFA because they have a higher threshold for manifesting a frontal lobe disorder with an equivalent amount of brain atrophy/dysfunction. Genetic factors related to frontal lobe development and aging are poorly understood, but biological differences related to FTD and SD need to be further explored based upon these preliminary epidemiological evaluations.

Another question related to demographics is the early age of onset for the FTLD patients. Because most studies are clinically but lack autopsy confirmation, it is hard to know whether this is truly an early age of onset disease. AD-type changes are protean, even in cognitively normal elderly and there are no highly specific protean markers for FTLD-related pathology making it hard to know whether FTLD is truly unusual after the age of 70, or just more difficult to diagnose. Gislason and colleagues suggest that frontal lobe presentations of dementia are common after the age of 80 years with nearly 15% of all dementia cases suffering from this cognitive pattern[23]. Some of the patients may suffer from AD, vascular disorders or dementia with Lewy bodies, others probably have a late-life onset of FTD. Clearly, more research into late-life presentations of FTLD is needed.

Diagnostic concerns

Mendez and others have expressed concern about many of the core and supportive items on the NC with regards to diagnostic specificity and the fact that few of the items have been operationalized. The core criteria for FTD, loss of social and personal conduct, emotional blunting and diminished insight are behavioral syndromes for which quantitative measures are still lacking. However, there are a wide-variety of new approaches to behavior which offer potential to improve the NC.

The Neuropsychiatric Inventory (NPI) is a scale that has been intensely studied in FTD[24] and definitely offers one potential way to evaluate behaviors described in the NC such as apathy, disinhibition, repetitive compulsive behaviors, and hyperorality. Emotional blunting is a complex syndrome with deficits related to emotional expression and emotional understanding both of which can be measured with neuropsychological and neurophysiological measures. Rosen and colleagues have found that both FTD and SD patients have profound deficits in emotional understanding using new scales that have now been available[25]. Similarly, Rankin has explored quantitative measures of insight in FTD[26].

Another problem with the NC is that some of the core and supportive criteria are misleading. For example, the EEG often shows subtle frontal or temporal slowing in FTD or SD[27], greatly negating the value of the "normal EEG" as an NC item. Similarly, prosopagnosia and visual agnosia are listed as core criteria for SD. Both develop in SD, often very late in the course of the illness. But, prior to these findings, profound deficits in emotional recognition are evident. Finally, the core features of PNFA capture many patients with left-sided predominant AD.

Future directions-FTLD research criteria

The maturation of the FTD field means that many groups across the world are beginning to study FTLD and related conditions. Opportunities for international research into risk factors, genetics and treatments are emerging. We believe that in order to facilitate this work, new research criteria for FTD are needed. These criteria should be based upon scientific evidence and should be easy to adapt in both the clinical and research environment. Additionally, these criteria should be cross-culturally valid. New scales that operationalize the abnormalities should be considered. Inclusion of corticobasal degeneration under the rubric of FTLD should be strongly considered. Finally, neuroimaging should be included due to the strong correlations between imaging patterns and neuropathology. The 2006 International FTD meeting represents an outstanding time to readdress diagnostic issues with this condition.

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