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Historical paper

Argentina's early contributions to the understanding of frontotemporal lobar degeneration

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ABSTRACT

Over a 100 years have passed since Pick's description of what is now termed frontotemporal lobar degeneration (FTLD). FTLD is a topic of intense current research interest yet some relevant contributions by non-English speaking authors have received little attention, which makes the history of FTLD research incomplete. In the hopes of filling some of the gaps in the history of FTLD research, the present article introduces fundamental work carried out in Argentina during the first half of the 20th century by Christfried Jakob and Braulio A. Moyano. Jakob's neurophilosophy, as well as his empirical descriptions on dementia and theoretic insights into the role of the frontal lobes are highlighted. Moyano's works on frontotemporal dementia (FTD), specifically concerning language deficits and the concept of focal pathology in Alzheimer disease presenting with progressive aphasia are introduced. These early contributions are examined in the light of the current knowledge on FTLD, highlighting some of the authors' early original contributions, as well as their misconceptions. These authors remain largely unknown despite the fact that their contributions were fundamental in kindling interest in behavioral neurology in Latin America, which continues to this day.

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1. Introduction

Fourteen years before the German physician Alois Alzheimer described the disease that later immortalized his name (Alzheimer, 1906), the Austrian-Jewish neurologist and psychiatrist, Arnold Pick, revealed to the scientific community a peculiar disorder characterized by progressive deterioration of language, as well as marked behavioral changes in association with focal lobar atrophy, later referred to as Pick disease (Pick, 1892; Todman, 2009). In another article published some years later, Pick described the clinical presentation of what we would nowadays call behavioral variant frontotemporal dementia (FTD) (Pick, 1904).

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Alzheimer's later contributions furthered knowledge of Pick disease. He developed novel neuronal staining techniques which he applied to cases with focal atrophy, thereby revealing the existence of spherical silver staining inclusions within neurones later called Pick bodies, as well as pale globular cells, termed Pick cells (Alzheimer, 1911).

Pick disease became a topic of intense interest among European neurologists of the day. Even in the early 20th century, controversy emerged concerning the correspondence between the label Pick disease (used to denote focal lobar atrophy) and the underlying pathology. A controversy which has continued to the present day.

Gans (1922), along with Onari and Spatz (1926), coined the term Pick disease which they sought to differentiate from "Common Senile Dementia" by means of the absence of senile plaques and Alzheimer's neurofibrillary tangles. The observation of histo-pathological changes similar to those of "Common Senile Dementia" in patients diagnosed with Alzheimer disease contributed to the belief that senile plaques and neurofibrillary tangles were specific characteristics of Alzheimer disease and not Pick disease. Subsequently, however, other authors such as Altman (1923), Kufs (1927) and Braunmühl (1930), recognized the presence of senile plaques in the brains of patients who had been diagnosed with Pick disease in life. As we shall see, the fact that neurofibrillary tangles may also be found in such patients was reported by the Argentinean physician, Braulio Moyano in 1931.

Much of the early work in the decades following Pick's descriptions has been forgotten and the period between 1930 and 1980 is generally regarded as "the dark ages" of dementia research. A renaissance of interest began in the 1980s led by the groups at Lund, Sweden, and Manchester, UK, culminating in the creation of the first clinical and research diagnostic criteria in 1994 under the name of FTD (Brun et al., 1994). Later, Neary et al. (1998) refined these previous criteria and renamed FTD as frontotemporal lobar degeneration (FTLD) taking into account the fact that a significant number of different entities (including semantic dementia and progressive non-fluent aphasia) were included under this umbrella term. More recently, a consortium of international researchers emphasized the need for validated and operationalized diagnostic criteria for the FTLD (Rascovsky et al., 2007).

Despite the lack of systematic publications in the English language during the "dark ages", some authors contributed to the understanding of Pick disease. Amongst them, we are especially interested in the research conducted by two physicians who worked in Argentina. First, we describe the work of Christfried Jakob, neurologist, psychiatrist and anatomic pathologist, born in Germany, but whose important research work was primarily carried out in Argentina, where he spent most of his life. Then, we explore the works of Argentine physician Braulio Aurelio Moyano, a student of Jakob.

2. Biographical notes

Christfried Jakob was born on December 25, 1866 in Wörnitzostheim, east of Nördlingen-im-Ries, Bavaria, Germany. He graduated from medical school at the University of Erlangen in 1890, the most distinguished student of his class. He wrote his doctoral thesis under the supervision of Friedrich Albert von Zenker, and worked at the Erlangen Medical Clinic, headed by Adolph von Strümpell.

In 1899, Jakob moved to Argentina, hired by the Foreign Affairs Ministry and under the initiative of the psychiatrist Domingo Cabred, to run the Laboratory of Anatomic Pathology at the Hospicio de las Mercedes. An important reason for leaving Germany was the promise that he would receive 300 post mortem brains annually, a number that surpassed that he could obtain in Germany. The Argentine government had originally offered the position to Strümpell, but he had refused.

Jakob worked in Argentina until 1910, when he moved back to Germany. He spent 3 years in his country of origin and subsequently, in 1913, he moved once more to Argentina where he lived until his death, in 1956. During this second period, Jakob was appointed Chief of the Neuropathological Institute at the Hospicio Nacional de Alienadas (which currently bares the name Hospital Braulio A. Moyano), and held many positions at the Universidad de Buenos Aires (UBA) and at the Universidad Nacional de la Plata. During his second period, all of his work was written and published solely in Spanish, a fact that almost certainly accounts for its neglect (Triarhou and del Cerro, 2006a, 2006b; Capizzano, 2006).

Braulio Aurelio Moyano, on the other hand, was born on August 21, 1906, in Villa Mercedes, San Luis, and died in 1959 in Buenos Aires, Argentina. Part of his medical education was carried out in Europe, where he met some of the most outstanding scientists at the time. In Argentina, he worked at the Hospital Nacional de Alienadas under Jakob's supervision, and he made important contributions to the field of neuropsychiatry, especially to the understanding of Pick disease and its language impairments.

3. Contributions to the understanding of the frontal lobes

3.1. *Jakob's neurophilosophy*

The frontal lobes have a major role in those behaviors usually considered as quintessentially human. Yet, they do not exert such actions in an isolated fashion but rather coordinated with other areas of the brain involved in information processing from the external and the internal *milieu*, and in concert with the emotional and motivational states. This statement, currently accepted among researchers working on the frontal lobes, reflects, although simplified, Jakob's neurophilosophical thinking.

In his article *Biological studies on the cerebral frontal lobes* (1906), Jakob expressed, based on his histological studies, that human behavior could not be explained on the grounds of the frontal lobes' intrinsic features and that, therefore, "the question concerning superior human functions cannot be answered pointing out their localization in one or another brain lobe but, instead, taking into account issues of another kind" (Jakob, 1906, p. 1373, "el problema de las funciones superiores humanas no está en su localización en tal o cual lóbulo cerebral sino en factores de otro orden"). Jakob was

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fascinated by phylogenetics and believed they were the means through which he could find the answer to the question of superior human functions, making a distinction between different attributes of human species and their corresponding phylogenetic correlates. He differentiated between the phylopsyche and ontopsyche, a topic later developed in his article *Progressive Dementia: A neurobiological analysis of Pick disease* (1946). The phylopsyche, he explains, includes a fraction of our brain activity inherited from more phylogenetically ancient species. Within it, he distinguished between two subcategories: the archipsyche, which contributes to the reflex functions, both visceral and somatic; and the paleopsyche, which contributes to the instinctual functions. The ontopsyche, on the other hand, allows us, according to Jakob, to elaborate an individual brain activity mediated, therefore, through "individual experience processes" ("procesos de experiencia individual"). According to Jakob, the latter is the most original phylogenetic acquisition of human brain, and it is necessary for its distinctive functions. Also referred to by the author as neopsyche, he further divided it into some other subcategories: the trophopsyche, an internal milieu regulator whose activity is carried out by the limbic system; the somatopsyche, an external milieu regulator whose activity is performed by the suprasylvian gyri; and the logopsyche, mediator of our symbolization of the world, through the perisylvian gyrus (Fig. 1).

This simplified model of Jakob's neurophilosophical thinking, presents a number of original features. For example, the ingenuity that allows him to address important questions about human nature from both a philosophical and neuroanatomical perspective. Also, Jakob's theories are similar to the famous "triune brain" hypothesis elaborated by Paul MacLean (1973). Nevertheless, it is worth highlighting some important differences between these two models. In Jakob's classification, for example, the different phylogenetic layers overlap anatomically and functionally, as he includes the limbic system within the neopsyche, contrary to Paul MacLean's triune brain, for which the limbic system is part of the old mammalian brain and not the neo mammalian brain.

Constantly placing a strong focus on the integration of information coming from the external and internal milieu, Jakob, in an article entitled *The mission of the frontal lobe towards a synthetic quantification of its production elements* (Jakob, 1949), points out two features of brain activity, the "internal" ("introyectal") and the "environmental" ("ambiental") aspects, that allow for the emergence of consciousness. According to Jakob, the frontal lobes share subcortical afferences and efferences that can be divided into a medial and a lateral portion. The medial, limbic, stream constitutes the so-called "internal" aspect. Its role is to carry visceral and motor sensitivity, creating the ground for elementary notions of vegetative well being and discomfort, hence contributing to affect. The lateral stream, on the other hand, constitutes its "environmental" aspect, related to praxias, or personal intervention, through its interconnections with the substantia nigra and the cerebellum. Both of them merge together giving birth to volition, also guided by gnosias as a result of postrolandic contributions.

This way, an affective (medial) contribution and an environmental-praxic (lateral) contribution, coexist in the frontal lobes. Both of them, through the "internal-environmental frontalization process" ("proceso de frontalización introyecto-ambiental") permit the elaboration of personal and conscious experiences. The "commemorative accumulation" ("conmemoración acumulativa") of such experiences allow an individual to plan and perform future actions. Such actions become the "learned volitive actions" ("acciones volitivas aprendidas"), which are remarkably related to the issue of free

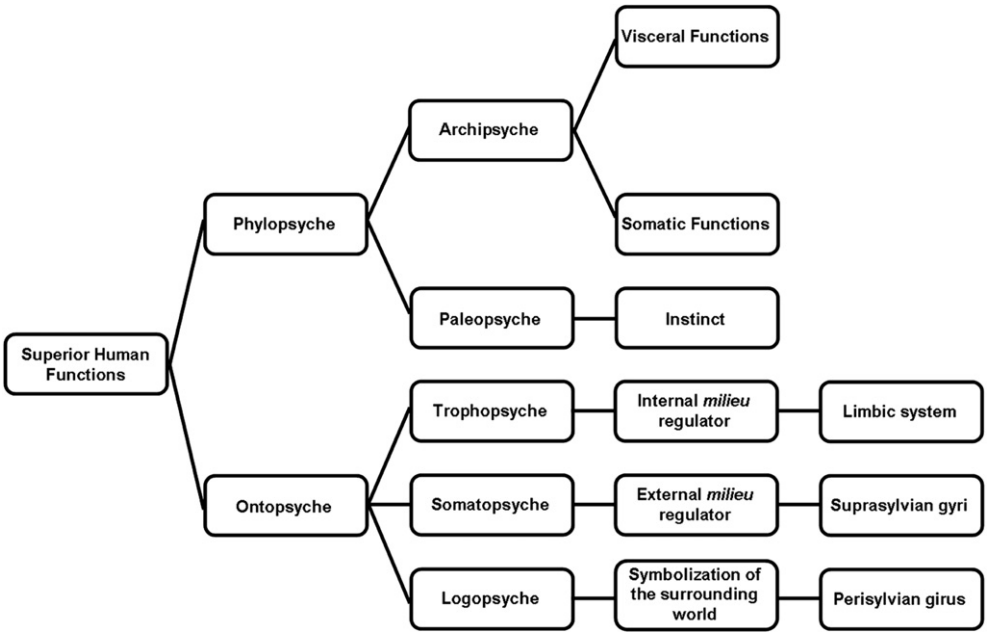

Fig. 1 – Simplified hierarchical representation of Jakob's phylogenetic model of the human brain. Based on the author's article *La demencia progresiva: Un análisis neurobiológico de la Enfermedad de Pick (Progressive dementia: A neurobiological analysis of Pick's disease)*.

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will. As highlighted elsewhere (Triarhou and del Cerro, 2006b), Jakob argued that "[…]it is mnemonic function that raises the cortical apparatus to its creative potential, its influence and dominant hierarchy in the psyche of the individual, liberates it from the ties of reflex law and elaborated instinct; that amplified expectation of action that we call volitional freedom consists of the possibility of anticipating the result of a given situation and selecting among various possibilities the one best suited to the momentary constellation and its individual advantage". In particular, this internal-environmental synthesis would explain, according to Jakob, the physio-psychological synthesis that enables joint work and mutual control of the spirit and the human body.

As early as 1911, Jakob described the limbic system as the visceral cortical centre that produces the internal feelings related to emotions (Jakob, 1911; Jakob and Onelli, 1911; Orlando, 1964). Within this system, he proposed the involvement of the cingulate cortex, the mammillary bodies, the mammillothalamic bundle and the thalamus, amongst others. These ideas herald those of James W. Papez (Papez, 1937), whose work on the limbic circuits were not published but until 1937 (Orlando, 1964; Triarhou, 2008, 2009).

Finally, to understand Jakob's neurophilosophy, it is necessary to take into account his interests in Kant's philosophy (Kant, 2004). As this philosopher, Jakob believed that human knowledge was mediated through a priori conditions, a human capability, independently of any experience, to perceive the world and make it comprehensible. The fact that such a priori conditions mediate our experiences, through their active participation, implies that they also partially create such experiences. In other words, we never know the object itself but the phenomenon instead, which we are able to perceive and think through our intuitions, such as time and space, and our categories, such as causality. These are the a priori conditions that, according to Jakob, constitute the main components of gnosias (Jakob, 1946).

4. Clinical description of FTLD and contributions to its histo-pathological characterization

In his 1946 article, Jakob hypothesed that Pick disease represents a model for progressive disintegration of a hierarchical cognitive system. He also emphasized the importance of longitudinal observation of patients.

The defect in Pick disease is not, according to the author, intellectual alone, but concomitantly affective, "because, at last, the most noble human ideals are not inspired or born from the intellect that realize them, but from the feeling that creates them" (Jakob, 1946, pp. 91–94, "porque, finalmente, se inspiran y nacen también los más altos ideales de la humanidad, no del intelecto que los realiza, sino del sentimiento que los crea"). According to Jakob, Pick disease results in the disruption between the paleopsyche, and the neopsyche, for the latter, according to the author's theory, creates individuality on the basis of instincts (paleopsyche) and reflexes (archypsyche). Such disruption implies, at the same time, the dissociation between the internal and environmental aspects, the subjective and objective world, respectively. This explanation of Pick disease seems parallels the aforementioned "internal-environmental frontalization process", explained in detail in his article *The mission of the frontal lobe towards a synthetic quantification of its production elements* (Jakob, 1949).

Another interesting article written by Jakob entitled *Frontocaudate symmetrical progressive encephalitis (A non-described form of atypical combined Pick Disease)* (Jakob, 1944) describes a young patient diagnosed with Pick disease.

35-year-old Argentinean woman who, prior to the onset of her disease, was effective, hard-working, neat and literate. Over a 9-month period (during which time she was pregnant), she showed symptoms including nervousness, depression, insomnia and headaches. This was followed by a lack of concern towards personal hygiene and reduced motivation. She had difficulty expressing herself, with word repetitions (perseveration) but preserved comprehension and memory. Neurological assessment was normal. With progression, the patient became indifferent, showing lack of concern for others and increasing apathy. Her thoughts dispersed and she showed inappropriate social behaviors with inane laughter and public nudity. Her memory began to deteriorate significantly and she completely abandoned all personal hygiene. The patient's language became stereotyped, with groaning, persistence of some phrases, teeth grinding, unstable walking and muscle rigidity. The patient died 4 years after the onset of her disease. Pathologic analysis of her brain demonstrated severe frontal lobe atrophy (with temporal lobes mildly flattened at the base), caudate nucleus atrophy, and significant damage of white matter. Cerebral vessels were spared. Microcopy demonstrated numerous plaques, granular bodies in white matter and partial atrophy of the hippocampus.

Jakob identified this case as a bifrontal type of Pick disease combined with striatal sclerosis (Fig. 2). The age of this patient, as well as the course of her disease, is somewhat surprising. While the mean age of onset for FTD is between 50 and 60 years old, pre-symptomatic family members of patient with an autosomal dominant FTD syndrome may show subtle cognitive and/or behavioral abnormalities even in childhood or adolescence (Geschwind et al., 2001; Boxer et al., 2005). Although information concerning the patient's family is limited, Jakob reports that her father committed suicide and her sister was admitted in that same hospital. It would be premature to conclude that this patient had an autosomal dominant FTD, nevertheless this is possible. Also, whereas the mean survival of FTD patients in one study was 6.1 ± 1.1 years old, those with motor impairment (like this patient showed) exhibited worse prognosis, and in the case of FTD associated with motor neuron disease, the mean survival was actually $3 \pm .4$ years old (Hodges et al., 2003; Boxer et al., 2005).

Turning now to the contributions of Jakob's protégé Braulio Moyano one must keep in mind two circumstances about his research: first of all, most of it was conducted while working in a major psychiatric hospital dedicated to "alienated" women; secondly, most of the cases were classified, by himself, as temporal variants of Pick disease.

Two of the most interesting articles published by Moyano were *Presenile Dementias. I. Alzheimer disease. II. Pick's atrophy* (Moyano, 1931) and *Histopathology of progressive and symmetric lobar sclerosis* (Moyano, 1932), respectively. These articles focus on the histo-pathological basis of Pick disease and the clinical manifestations of focal lobar atrophy. With

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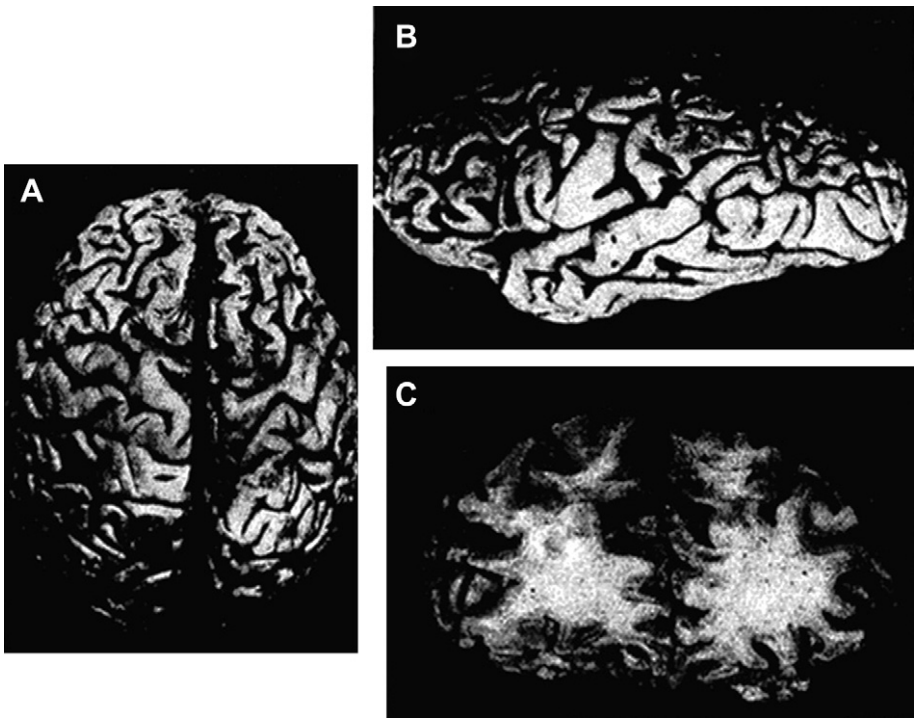

Fig. 2 – Anatomo- and histo-pathological analysis of Jakob's case of frontocaudate symmetrical progressive and atypical combined Pick's disease. (A) Notable sclerotic bifrontal atrophy. (B) Lateral view of left hemisphere showing marked frontal sclerosis and mild basal temporal sclerosis. (C) Coronal slice of frontal loves revealing cortico-subcortical sclerotic atrophy. Adapted from Jacob.

respect to its histopathology, Moyano reviews the literature and points out that, until then, it was believed that neurofibrillary tangles were specific features of "Common Senile Dementia" and Alzheimer disease. He describes the presence of neurofibrillary tangles in patients diagnosed with Pick disease and concludes that neurofibrillary tangles may be present in patients with focal lobar atrophy, a fact that was overlooked until very recently (McKhann et al., 2001; Cairns et al., 2007).

In terms of clinical features, he describes an insidious onset, beginning between ages 50 and 60, with the first manifestations reflecting the distribution of the disease. In the frontal variant, a lack of initiative dominates, patients remain isolated from others, unaware of their situation and, finally, all voluntary actions vanish. In the temporal variant, on the other hand, the most characteristic feature is "amnesic aphasia", an inability to name objects with spared capacity to recognize them (in other terms, anomia without agnosia). To overcome their impairment, patients tend to describe the use of the objects and offer circumlocutions. In other cases, Moyano explains, difficulties arise in phrase construction, leading to marked agrammatism.

Moyano's explanation for the "amnesic aphasia" was that "it represents early compromise of Wernicke's area" (Moyano, 1932, p. 258, "exteriorize el primer grado de sufrimiento de la zona de Wernicke"). With progression, however, there is severe damage of the language area, turning the "amnesic aphasia" into full blown Wernicke's aphasia. Ultimately, language becomes completely incomprehensible.

Almost two decades later, Moyano published another article, entitled *Clinical aspects of Pick's atrophy (Circumscribed atrophy of the brain). On the disintegration of language functions* (Moyano, 1951), in which he provides a detailed description of the clinical manifestations resulting from damage to each of the brain lobes most frequently affected in this disease. Again, the emphasis is on the impact of damage to the temporal lobes. He mentions that the end stages of Pick disease may result in complete aphasia, both receptive and expressive, as a consequence of bilateral temporal damage, even with an intact Broca's area. In this article, Moyano also highlights the existence of a region in the brain dedicated to memory storage of words, pointing at the posterior two thirds of the lateral aspect of the temporal lobe as its location. These observations herald much contemporary work on the role of the basal temporal lobe in lexical and semantic processes (Kopelman, 2002; Damasio et al., 2004).

One of the cases described reported by Moyano, Rosa, an Argentine 68 year-old single woman presented with fluent language conversational, anomia, marked pauses, circumlocution, and phonological paraphasias but spared grammatical structure. Articulatory impairment was not evident. She had impairment of word comprehension for parts of the body but other domains appeared spared, although they were assessed with few images of high frequency of items. Comprehension and execution of simple orders, mostly regarding the patient's own body, showed impairment. Naming of objects was severely impaired. Moyano was not able to identify behavioral changes until late in the disease. Moyano's diagnosis was

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temporal variant Pick disease, which was supported by pathological examination showing temporal lobe atrophy as well as mild parietal involvement, predominantly on the left side. This language syndrome clearly corresponds to what is currently referred to as primary progressive aphasia (PPA). Beyond that assertion, classification of the subtype of PPA is difficult. Classical features of semantic dementia (severe global word comprehension deficits) were absent and presence of phonological errors might suggest so-called logopenic progressive aphasia but the lack of reference to syntactic comprehension in his description makes it very difficult to be certain (Gorno-Tempini et al., 2004, 2008).

In the 1951 article he also emphasied the relevance of differentiating between the manifestations of injury at the convexity (which he also refers to as the prefrontal cortex) compared to the orbital surface of the frontal lobes. The former would seem to feature impulse control impairments, lack of initiative, lack of judgement, as well as disturbances in logical associations, while the latter results in impaired emotions, which become evident through changes in personality.

5. Reinterpreting modern definitions through the analysis of concepts taken from the past

Many of the ideas proposed by C. Jakob and B. Moyano were original. For example, Jakob's neurophilosophical model that highlighted the relevance of an integrated system consisting of an "internal" and an "environmental-praxic" aspect of the frontal lobe connections, for the individual elaboration of conscious experiences and the execution of conscious actions. Under the "internal" aspect, he included the elaboration of elementary notions of vegetative well being and discomfort, conferring it an affective value and associating it with the limbic system as its neural substrate. This resembles in many ways Damasio's (1994, 1996) somatic marker hypothesis. Jakob ventured into notions of free will as early as the 30s, pioneering in a field that has gained increasing attention in cognitive neuroscience in the past decade. As for Moyano's work, besides his anatomoclinical descriptions and neural correlations with symptoms, he observed that patients with focal lobar atrophy may have neurofibrillary pathology, characteristic of Alzheimer disease.

One can detect from their early work many of the core features of what is nowadays known as behavioral variant FTD: behavioral changes, including social isolation, indifference, and disinhibition. Perhaps the most prominent criticism that could be made to the works by Jakob and Moyano is the use of ambiguous terms, the limited systematization of their method, and the relatively poor examination of cognitive and emotional states of patients. Besides this shallow criticism, one must understand that in the first half of the 20th century, two physicians devoted to the study of FTLD in Latin America working in relative isolation were able to make contributions that were later replicated in the literature, when the advancement of technology allowed for the development of new techniques to explore the anatomy, histology, neuropsychology, and behavior of patients with degeneration of the frontal and temporal lobes.

It is also interesting to mention that in the case of Moyano's work, it was strongly committed to understanding progressive language disorders. The clinical features of the disease were exclusively explained in terms of damage to Wernicke's area. Nowadays, this turns out to be insufficient in order to explain, at least, the amnesic aphasia of the semantic dementia (SD), which we now conceptualize on the basis of damage to the polar and inferior temporal lobe (Snowden et al., 1989; Hodges et al., 1992; Neary et al., 2005). Moyano might have also recognized a variant which is now termed logopenic progressive aphasia. Of course, many years had to elapse for the field of dementia to start systematizing the different symptomatic profiles of frontal and temporal variants of FTLD (Snowden et al., 1989, 2002), particularly the subtypes of primary progressive aphasia as an umbrella term comprising SD and progressive non-fluent aphasia (Mesulam, 1982; Mesulam et al., 2003).

6. Conclusions

In spite of the limitations that characterized the research scene in Latin America during the first half of the 20th century, as well as the more limited knowledge and technology existent at that time, the present article reveals that authors devoted to the study of Pick disease managed to create pioneering paradigms and fundamental theoretical and clinical descriptions to our understanding of FTLD. While their work was mostly confined to the Spanish-speaking medical community, these authors contributed with original knowledge and were very influential teachers for the generations to come, becoming valuable figures in the Latin American history of medicine and medical research.

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