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The Frontotemporal Dementias: An Update

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Abstract

The diagnostic criteria for frontotemporal dementia (FTD), revised in 2011, make it possible to differentiate three levels of diagnostic certainty: possible, probable or certain. However, it is still sometimes difficult to distinguish it from other conditions such as psychiatric diseases. In recent years, genetic and molecular research has grown considerably. The ten or so mutations discovered over the past 15 years gradually lead to more precise phenotypes. Therapeutically, memantine, which had given hope, is abandoned. There remain the classic serotonin reuptake inhibitors, which only temporarily relieve the important burden of the caregiver. The evolution of DFT is faster than that of Alhzeimer's disease, especially when it is associated (in 15% of cases) with motor neuron involvement. Therapeutic hope currently rests on possible modifying disease treatments that could result from current and future genetic discoveries.

Keywords

Frontotemporal dementia; Clinical features; genetics; Behavior; Treatment

Introduction

In 1998, the generic term frontotemporal dementia (FTD) was proposed [1], in order to gather, on the basis of close epidemiological, clinical and neuroradiological characteristics, all the focused atrophic processes affecting the frontal and/or temporal lobes to simplify the nosological approach. Frontotemporal dementia is a group of neurodegenerative diseases characterized by behavioral and language disorders associated with deterioration intellectual (referred to as "dementia" from a certain threshold of severity). They are due to the progressive deterioration of certain areas of the brain (frontal zones and temporal) [2]. FTDs are serious diseases that reduce the life expectancy of people reached. The prevalence (number of patients affected at one time) of FTD varies between 1 in case 6,000 people and 1 in 30,000 depending on age (it increases with age). The DFT reach both men and women. Although it can appear at any moment during adult life, it occurs most often between 50 and 60 years [3]. Several mechanisms may be involved in FTDs, but the cause (s) of these diseases is unknown. As the term "fronto-temporal" indicates, these are the parts of the brain called frontal and temporal lobes which are damaged. The parietal lobe can sometimes be reached too. Neurons located in these regions lose their function and die, for reasons still unknown.

There are three subtypes of FTD [4]. The symptoms are the same, but these types of FTDs are distinguished by the nature of lesions found in the brain, which cannot be identified than at the autopsy. In 60% of cases, the lesions observed are due to the accumulation of protein in neurons, the nature of which is not yet known. These accumulations, called inclusions, are toxic to neurons. In other cases, we observe inclusions consisting of an abnormal form of a protein called tau protein. These inclusions often have a particular aspect designated by the term "Pick's body": these bodies cause the neurons to swell and then degenerate. The presence Pick's body defies the subtype of DFT called Pick's disease. Finally, more rarely, no particular lesion is identified; even if the neurons degenerate and also die (we talk about cerebral atrophy). It is then DFT without specific histological sign [5].

In addition, there are some genetic forms of FTD that affect multiple members of the same family (family forms). Some genetic forms are due to mutation of the tau gene, resulting in the production of abnormal tau proteins causing damage in neurons. A second gene, the pro granulin gene, has recently been cause in some family DFTs, although the mechanisms. These two genes are responsible for about 30% of family forms of FTD. Finally, two other responsible genes are known (the VCP and CHMP2B genes), but they seem very rarely involved [6].

What are the Manifestations?

At the beginning, the FTP is essentially manifested by behavioral and language that appear together or successively in time, and are very variable from one patient to another. Most often, behavioral disorders are predominant. When language disorders are the most important, we speak of progressive aphasia or semantic dementia.

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Behavioral disorders

In the first phase of the disease, the person seems normal but develops mild behavioral disorders, resulting in surprising reactions that are often attributed by family or friends to stress, fatigue or depression. At the beginning, the FDT can manifest itself in a phase of "intellectual fatigue" (apathy) and indifference to emotion, desires and surroundings [7]. Affected people seem disinterested in everything, including their loved ones, and fall back on themselves. They no longer have initiative or motivation, neglect their responsibilities and some patients even tend to lie down. This state is often wrongly attributed to a depression. In other cases, behavioral disorders are more dramatic. Thus, some affected persons act in a clearly uninhibited manner, that is, without account of the notion of prohibition or inconvenience. The patient can, for example, undress in public, to say too familiar to people he knows little or unknown, become coarse. In fact, the people affected have difficulty in respecting the practices of "good social behavior: they sit badly at the table, make inappropriate jokes or inappropriate reflections, urinate in public, drive fast without respecting the signs, do not pay for their purchases.

Patients can also start acting strangely (repeat continuously the same actions) or scrupulously follow rituals or habits fixed time. They can make a fixation on certain objects, that they start to collect, or on certain hobbies that they practice then in an extreme way (casino, games, crosswords…). In the advanced stages of the disease, some people put objects in their mouth in a compulsive way. Most sufferers are unable to concentrate, even in important circumstances (as in the case of doctor for example). Some patients are more likely to be aggressive or even violent, with asocial. They lack patience and are easily irritable [8].

Finally, running away is common, but patients are usually not disoriented (they do not get lost), at least at the beginning of the disease. They may feel a need incessant to move, and so walk decisively for miles, without want to go to a specific place. The patient does not complain about his behavior problems, but he can complain about headaches or possibly imaginary stomach ache, or being convinced that he is suffering diseases he has not yet (hypochondria). The eating behavior also changes in the majority of patients. Numerous are those who are constantly snacking or eating an unusual voracious appetite, or still discover a new attraction for the alcohol, consumed suddenly of excessive way. Some people may even go from an uncontrollable need to food (bulimia) with no appetite (anorexia), without transition. Because of these dietary changes, weight gain is common [9].

In addition, many patients neglect their personal hygiene (wear dirty clothes, wash less ...) as well as that of their place of life (no longer do the housework). Unlike Alzheimer's disease, which is another form of dementia, disorders of memory do not occur at the beginning of the disease. Similarly, the patients do not have special difficulties in using everyday objects or getting dressed. Depression and inability of the person to retain urine or stool (incontinence) may exist at this stage. There may also be difficulties in the management of money and some patients must quickly be placed under guardianship financial [10].

Language disorders

Language disorders can range from a decrease to a total absence of speech in the advanced stages of the disease (the person becomes dumb). A tendency to repeat systematically the end of his interlocutor's sentences, as an answer (echolalia), can appear. People with FTD may have difficulty following a series of ideas or to maintain any conversation. Some patients seek their words or have difficulty articulating and gradually lose speech, but their understanding is preserved (at least in the beginning). We then speak of progressive aphasia [11]. Their vocabulary is rapidly getting poorer, and reading and writing are also sources of difficulties. On the other hand, other patients will have no difficulty in pronunciation, but they will have problems of comprehension and identification of objects, which they will not understand more the function [12]. For example, if we talk about the word "dog", the patient can ask what a dog is, no longer understanding the meaning of the word. In this case, we speak of "Semantic dementia" (semantic memory is the memory of the meaning of words, of function of things). Subsequently, there is a gradual confusion, the loss of any capacity to reasoning and memory problems. The disorders of judgment and rigidity of the thought are also features. Patients become unable to program an activity, or to do simple things [13].

Movement disorders

Rigidity of movements and gait disorders sometimes follow, at a late stage of the disease. In family forms, which generally begin earlier in life (around age 40), the disease may not be manifested in the same way in the different members of the family. It is sometimes accompanied by symptoms similar to those seen in Parkinson's syndrome, including rigidity, difficulty to walk and early speech disorders [14].

What is the Evolution of FPDs?

The condition of the patient deteriorates inexorably, over several years [15]. He gradually becomes incapable to wash or dress alone; he loses the meaning of the objects that are in his environment, and sometimes has trouble identifying relatives. Urinary incontinence, sometimes fecal (inability to retain urine and stool), affects many patients. They become unable to speak [16] and do not react to external noises, sometimes keeping their eyes closed. They stay either seated or laying down if no one helps them get up. At this stage, patients have difficulty in properly swallowing water and fluids (disorders swallowing). In the long term, the hands and sometimes the legs become paralyzed. The patient thus becomes totally dependent, and needs permanent help for every gesture of everyday life: walk (when possible), toilet, clothing or food. Some patients may then be placed in institutions specialized. Life expectancy, from the moment of diagnosis, is on average ten years, but there is great variability and it is impossible to predict the evolution of the disease.

How to Explain the Symptoms?

The parts of the brain that are destroyed or damaged in the FTPs are the frontal lobes and the temporal lobes. The frontal lobes are the seat of reasoning, abstract ideas and planning [17]. They also intervene in the modulation of emotions and the personality in general, hence the problems of behavior. In addition, part of the left frontal lobe is involved in the transformation of thoughts into words, which partly explains the language disorders. Motor disorders or irrepressible urge to walk are also linked to the frontal lobes. The temporal lobes play a role in the formation and remembrance of memories. They also distinguish the tone and intensity of sounds, and understand the meaning of words. These essential functions in the relational and social behavior of the person gradually deteriorate during the FTD, as the neurons responsible for these functions die or lose their functionality.

How is One Diagnosed with FTD?

Diagnosis is usually difficult to do because behavioral disorders are misleading and often lead to psychiatric consultation at first. In adapted neurology consultations, different tests are made to evaluate memory, speech, comprehension, movements, and mood. Then, the diagnosis of FTD can be confirmed by magnetic resonance imaging (MRI) or CT scan [18]. These are painless examinations to study the brain with great precision and highlight the presence of atrophy, that is to say, degeneration, frontal and temporal lobes. Sometimes, at the very beginning of the disease, other examinations may be necessary to make the diagnosis because atrophy is not obvious. The cerebral scintigraphy or SPECT (single photon emission scans) is an imaging technique giving an idea of brain activity [19]. In the FTD, it shows a decrease in blood flow and frontal and temporal lobe activity. This examination is performed after injection into a vein of a product which is preferentially fixed in the brain areas which are the seat of intense activity. Positron Emission Tomography (PET) is another test for visualizing brain activity, but it is less accessible because it is very

expensive. Finally, a lumbar puncture can be performed. It consists of taking the fluid circulating around the spinal cord (the cerebrospinal fluid) in the lower back of the spine. The analysis of the cerebrospinal fluid ensures, among other things, that the neurological disorders are not due to infection or Alzheimer's disease. However, it is difficult to distinguish the different FTDs between them (Pick's disease or FTD without accumulation of Pick's body in the neurons). Indeed, the detection of Pick's body can only be done at the time of the autopsy (when the patient did not register in the organ rejection register). Most often, only the diagnosis of FTD can be made, without type precision [20].

Can We Confuse These Diseases with Others?

FTDs can be confused with many other neurological diseases, but also with psychiatric disorders, especially at the beginning. Indeed, the changes of behavior are often attributed to stress or depression, before being considered as of neurological origin. It can also be considered a disease psychiatric (bipolar disorder, obsessive-compulsive disorder) or as the consequence alcoholic beverages, while this is a symptom of FTD. Subsequently, several diseases responsible for dementia or disorders of language and movement can be evoked, such as a tumor in the frontal lobe, atrophy multi-systematized (AMS) and especially Alzheimer's disease.

Alzheimer's disease, which is the first cause of dementia, differs from FTDs among others by disorders of memory marked from the beginning of the disease, by a later start, and by disorientation in the earlier space [21]. Some "accidents" or abnormalities can also cause these symptoms: trauma cranial, stroke (rupture or obstruction of a vessel in the brain), excess fluid in the brain (hydrocephalus). Finally, certain diseases of infectious origin such as meningitis or brain inflammation (encephalitis) due to AIDS or herpes virus may look like FTD. In all cases, the results of MRI, lumbar puncture or the evolution of symptoms allow the neurologist to make a difference.

Genetic Aspects

In the majority of cases, FTDs are sporadic, that is, they occur in a family that has never experienced a similar case [22]. Nevertheless, there are a significant number of family cases of FTD (at least 30% of cases). In familial cases, the disease may be due to at least four known genes (the tau gene and the progranulin gene, and more rarely the VCP and CHMP2B genes) [23]. Most often, the genetic anomaly seems to be transmitted from generation to generation (autosomically dominant). A patient then has a risk in two to transmit the disease to his children, regardless of gender. However, there are still many unknowns about the genetic aspects of FTDs, and their mode of transmission from one generation to the next is not always clearly defined. In all cases, it is therefore recommended to consult a medical genetics center for a family risk assessment [24].

Is there a Treatment for this Pathology?

At the present time, there is no treatment that can heal finally or slow the evolution of FTD when memantine failed to be active [25]. Most often, the treatment of FTD is to alleviate the patient's behavioral problems. For example, drugs that work against depression or anxiety may be effective, including trazodone. In particular, trazodone makes it possible to act effectively on the incessant desire to move, on the increase of appetite, irritability and mood disorders. It can also improve the quality of sleep, disrupted by the disease [26]. Other drugs of this type (called serotonergic) are sometimes offered [27]. In the same way, other drugs to improve sleep (hypnotics), to calm agitation (sedatives), depression (antidepressants) and anxiety or aggressiveness (some antipsychotics) can sometimes be tried. Medications prescribed for Alzheimer's disease to limit intellectual deterioration (cholinesterase inhibitors) have no effect in FTDs and may even aggravate behavioral problems.

What are the Other Therapeutic Options?

Speech therapy can help maintain language and prevent (or delay) the occurrence of dangerous swallowing disorders. Speech-language therapy is all the more important because language disorders can prevent the patient from expressing themselves clearly, which can accentuate his behavioral problems (aggressiveness, anger, etc.). If possible, an activity carried out as part of a reception or a day hospital must be set up, since a new environment, different from the home, can often reduce behavioral disorders [28]. Indeed, these day structures will offer therapeutic and relational care essential to the quality of life of the sick person. These treatments can significantly improve the behavioral disorders, which allow the patient to stay more easily in his family. However, they do not allow maintenance or return of autonomy, illness always leading to take over.

Is Psychological Support Desirable?

Psychological support is especially necessary for relatives because people with FTD are not particularly aware of being sick. Nevertheless, they appreciate being, over the years, a trusted medical reference to exploit their behavioral changes. In some cases, the psychologist can be used to mediate between the patient and his family, to facilitate relationships and to better understand the disease. The relatives, as for them, quite throughout the illness, first because of the change of behavior that generate interpretations ("he/she does not love me anymore", "he/she becomes alcoholic or depressed. They are difficult to accept, and the patient quickly becomes indifferent, disinterested in his family, family affairs, which is particularly painful for the sick person, the reduction of verbal pressure and therefore of communication. and the gradual loss of autonomy are sources of anxiety, distress and helplessness, so family members need psychological support that also enables them to cope with new responsibilities (providing care, make the decision to place the patient in the specialized institute) and the feeling of guilt that often survive [29].

What are the Consequences of the Disease on Family, Professional, Social and Sporting Life?

The DFT completely disrupts the life of the patient and that of his family, on all levels (family, financial, professional). Gradually, budget management, purchasing, use of means of transportation, personal care including personal hygiene and taking medication require the assistance of a loved one. Driving is fast becoming dangerous. Because of the behavioral disorders, the entourage is brought to closely monitor the patient who can be aggressive, angry or completely indifferent and unaware of the danger. These behavioral problems are very difficult to support for those close to them, who must "cash in" the tantrums as well as the total indifference. They are often responsible for social isolation, as friends and sometimes the family does not always understand that the "deviations" of the person (bad joke, coarse or aggressive language) are due to his illness and are not intentional. Obviously, the professional activity can no longer be assured. The patient, for his own protection, must generally be placed under judicial guardianship. The guardian, often a member of the family, has to take care of the patient's financial management, from daily purchases to the management of the bank account. When the disease progresses, the patient gradually lose his autonomy and become unable to carry out daily actions (toilet, meal...). In order to alleviate the burden of maintaining the patient at home, outside interventions (nursing services, nursing care, home help, domestic help or placement in a specialized institute) can be put in place [30]. These periods of "respite" for loved ones are absolutely essential. But sometimes the care givers need some treatments with SSRIs!

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