DAC Scientific Update

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Development of disease-modifying therapies for frontotemporal dementia

This update is based on the review of 2 publications :

- Panza, F., Lozupone, M., Seripa, D. et al. Development of disease-modifying drugs for frontotemporal dementia spectrum disorders. Nat Rev Neurol 16, 213–228 (2020). https://doi.org/10.1038/s41582-020-0330-x

- Bradley F Boeve, Adam L Boxer, Fiona Kumfor, Yolande Pijnenburg, Jonathan D Rohrer.Advances and controversies in frontotemporal dementia: diagnosis, biomarkers, and therapeutic considerations.www.thelancet.com/neurology Vol 21 March 2022

I) KEY POINTS

- Frontotemporal dementia (sometimes referred to as FTD) is an umbrella term for a group of rare neurodegenerative brain

disorders that primarily affect the frontal and temporal lobes of the brain.

- Frontotemporal dementia is caused by an abnormal accumulation of proteins in the frontal and/or temporal lobes of the brain.

- In frontotemporal dementia, changes to nerve cells in the brain's frontal lobes affect the ability to reason and make decisions, prioritize and multitask, act appropriately, and control movement.

- The first noticeable symptoms of frontotemporal dementia are changes in personality and behaviour and/or difficulties with language.

- Despite often being considered a rare disease, scientists think that **frontotemporal dementia is the most common cause of dementia in people younger than age 60.** Although the age of onset ranges from 21 to 80, the majority of frontotemporal dementia cases occur between 45 and 64.

- People can live with frontotemporal disorders for up to 10 years, sometimes longer, but it is difficult to predict the time course for an individual patient.

- The symptoms of frontotemporal disorders gradually rob people of basic abilities: thinking, talking, walking, and socializing. They often strike people in the prime of life, when they are working and raising families. Families suffer, too, as they struggle to cope with the person's daily needs as well as changes in relationships and responsibilities.

- Many healthcare professionals are not familiar with frontotemporal dementia which is frequently misdiagnosed as

Alzheimer's disease, depression, Parkinson's disease, or a psychiatric condition. On average, it currently takes 3.6 years to get an accurate diagnosis.

- Symptomatic treatments have limited benefits and can exacerbate symptoms
- No cure or treatments that slow or stop the progression of frontotemporal disorders are available today.
- An increased understanding of frontotemporal disorders is helping the development of disease-modifying therapies.
- Several potential disease-modifying therapies have been or are being tested in early clinical trials.
- Several challenges must be overcome to recruit homogenous patient cohorts and ensure that appropriate biomarkers and

clinical endpoints are used so that clinical trials produce meaningful results.

2) Additional Information on Frontotemporal Dementia

The information presented is based on the review of Patient Associations and Governments websites (see Resources).

2.1: Clinical Variants

- Frontotemporal dementia affects everyone differently. Its symptoms vary a lot and depend on which areas of the frontal

and temporal lobes are damaged – and so the type of frontotemporal dementias the person has.

- Several clinical variants of frontotemporal dementia have been identified :
  - **Behavioral variant frontotemporal dementia (bvFTD)**

    It is the most common form of frontotemporal dementia and it involves changes in behavior, judgment, and personality.

    People with this disorder may have problems with cognition, but their memory may stay relatively intact. They may do impulsive things that are out of character or may engage in repetitive, unusual behavior.

    People with behavioral variant frontotemporal dementia also may say or do inappropriate things or become disinterested in family or activities that they used to care about. Over time, language and/or movement problems may occur.

    In the past, behavioral variant frontotemporal dementia was called Pick's disease, named after the scientist who first described it in 1892.

    Some individuals who meet diagnostic criteria for behavioural-variant frontotemporal dementia have a very slow disease course (over decades) with slow progression of cognitive impairment and often normal brain imaging studies (MRI, PET). Their disease is classified as **frontotemporal dementia phenocopy.**

- **Primary progressive aphasia (PPA)**

  It is the second most common form of frontotemporal dementias and involves progressive changes in the ability to speak, write, read, understand and express thoughts and/or words.

  Problems with memory, reasoning, and judgment can develop and progress over time. Sometimes a person with primary progressive aphasia cannot recognize the faces of familiar people and common objects. Other individuals have increasing trouble producing speech and may eventually be unable to speak

- **Movement disorders :**

  In addition to the variants mentioned above, three additional variants (frontotemporal dementia spectrum motor syndromes) are accompanied by movement abnormalities .

  Two of these disorders — **progressive supra-nuclear palsy(PSP)** and **corticobasal syndrome (CBS)** — involve parkinsonism. (slow movement, impaired speech, muscle stiffness, involuntary shaking)

  The third motor syndrome is **amyotrophic lateral sclerosis–frontotemporal spectrum disorder (ALS–FTSD),** which is characterized by frontotemporal dysfunction in association with amyotrophic lateral sclerosis.

2.2 Causes (Neuropathological Process). :

Frontotemporal lobar degeneration (FTLD) is not a single brain disease but rather a family of brain diseases that share some common molecular features. Scientists are beginning to understand the biological and genetic basis for the changes observed in brain cells that lead to frontotemporal lobar degeneration.

Scientists describe frontotemporal lobar degeneration in terms of patterns of change in the brain seen in an autopsy after death. These changes include loss of neurons and abnormal amounts or forms of **proteins called tau** and **TDP-43**. These proteins occur naturally in the body and help cells function properly. When the proteins don't work properly and accumulate in cells, for reasons not yet fully understood, neurons in specific brain regions are damaged.

In most cases, the cause of a frontotemporal disorder is unknown. Individuals with a family history of frontotemporal disorders are more likely to develop such a disorder. About 10 to 30 percent of behavioral variant frontotemporal dementia is due to specific genetic causes.

Frontotemporal disorders that are inherited or that run in a family are often related to mutations (permanent changes) in certain genes. Genes are basic units of heredity that tell cells how to make the proteins the body needs to function. Even small changes in a gene may produce an abnormal protein, which can lead to changes in the brain and, eventually, disease.

Scientists have discovered several different genes that, when mutated, can lead to frontotemporal disorders the 2 most frequent are :

- **Tau gene** (also called the **MAPT gene**)—A mutation in this gene causes abnormalities in a protein called tau, which forms tangles inside neurons and ultimately leads to the destruction of brain cells. Inheriting a mutation in this gene means a person will almost surely develop a frontotemporal disorder, usually behavioral variant frontotemporal dementia, but the exact age of onset and symptoms cannot be predicted.

- **GRN gene**—A mutation in this gene can lead to lower production of the protein **progranulin**, which in turn causes another protein, **TDP-43**, to go awry in brain cells. Many frontotemporal disorders can result, though behavioral variant frontotemporal dementia is the most common. The GRN gene can cause different symptoms in different family members and cause the disease to begin at different ages.

2.3 Diagnosis :

Frontotemporal disorders can be hard to diagnose because their symptoms—changes in personality and behavior and difficulties with speech and movement—are similar to those of other conditions. For example, behavioral variant frontotemporal dementia is sometimes misdiagnosed as a mood disorder, such as depression, or as a stroke, especially when there are speech or movement problems. To make matters more confusing, a person can have both a frontotemporal disorder and another type of dementia, such as Alzheimer's disease. Also, since these

disorders are rare, physicians may be unfamiliar with their symptoms and signs.

Getting the wrong diagnosis can be frustrating. Without knowing their true condition, people with frontotemporal disorders may not get appropriate treatment. Families may not get the help they need. People lose valuable time needed to plan treatment and future care.

Researchers are studying ways to diagnose frontotemporal disorders earlier and more accurately and to distinguish them from other types of dementia. One area of research involves biomarkers, such as proteins or other substances in the blood or cerebrospinal fluid, which can be used to measure the progress of disease or the effects of treatment. Also being studied are ways to improve brain imaging and neuropsychological testing.

2.4 Treatment :

- There's currently no cure or specific treatment for frontotemporal dementia.

- **Drugs used to treat or slow Alzheimer's disease don't seem to be helpful for people with frontotemporal dementia**, and some may worsen the symptoms of frontotemporal dementia.

- Certain medications can help manage symptoms of frontotemporal dementia :

- **Antidepressants.** Some types of antidepressants, such as trazodone, may reduce the behavioral problems associated with frontotemporal dementia. Selective serotonin reuptake inhibitors (SSRIs) — such as citalopram (Celexa), paroxetine (Paxil) or sertraline (Zoloft) — also have been effective in some people.
- **Antipsychotics.** Antipsychotic medications, such as olanzapine (Zyprexa) or quetiapine (Seroquel), are sometimes used to treat the behavioral problems of frontotemporal dementia. However, these medications must be used with caution in people with dementia due to the risk of serious side effects, including an increased risk of death.

3) Disease-modifying treatments in development.

- A disease-modifying treatment is a treatment that has the potential to affect the biological abnormalities responsible for frontotemporal dementia and have a positive impact on the evolution of the disease.
- In the past decade, researchers have developed a better understanding of the biological changes in the brain that lead to frontotemporal disorders.
- This knowledge has led to the identification of several potential disease-modifying drugs that are being studied in patients however, no clear-cut therapeutic agent has yet emerged from the ongoing conduct of clinical trials.

- **Most current therapeutic trials target the genetic forms of Frontotemporal dementia :**

  - Proganulin deficiency is observed in patients with a mutation in the GRN Gene. Therapeutic interventions raising proganulin concentrations in blood and CSF are actively being studied.

  - **Gene therapy : 2 pharmaceutical companies have recently announced the start of GRN gene therapy programmes.**

- **Frontotemporal lobar degeneration with Tau pathology :**

- Based on a better understanding of the biological anomalies affecting Tau during frontotemporal lobar degeneration researchers are following many potential therapeutic approaches targetting TAU pathology..

- The following list is an illustration of the depth of the ongoing research program :

  Inhibition of tau aggregation

  Inhibition of tau acetylation

  Clearance of tau aggregates

  Microtubules stabilization

- For each of these approaches, the therapeutic interventions that are being investigated include anti-inflammatory agents, vaccines, antibodies and neuroprotective peptides.

- **Targeting TDP43**

- Clinical development programs aiming at reducing the accumulation of TDP43 in the brain of patients presenting with FTD are not as advanced as with Tau. However, there has been significant progress made over the recent years to identify potential targets and this should translate into a more comprehensive clinical program in the future.

- **The lancet review (March 2022) lists more than 20 ongoing clinical trials with potential disease-modifying therapeutic agents for frontotemporal dementia.**

- Unfortunately, the first series of clinical trials that have been completed have all had negative outcomes either for lack of efficacy or potential safety concerns with the treatment being studied.

4)Clinical trials challenges

- The nature of frontotemporal dementia presents the research communities with several challenges that need to be addressed for disease-modifying therapies to reach clinical practice :

- Trials must be designed in a way that clinical benefits to be detected.
- Enough patients need to be found to participate in new studies.
- Differentiating between the subtypes of FTD to select homogenous patient groups for the conduct of new studies.
- Identification of biomarkers that can differentiate between subtypes.
- Availability of clinical scales that can capture disease progression and clinical change in a short period of time.
- Study endpoints must be meaningful to all study participants despite their variety of symptoms.

In order to address these challenges, the research community has created a series of large international natural history cohorts of frontotemporal dementia such as :

The Genetic FTD Initiative (GENFI) , a European and Canadian study focusing on both pre-symptomatic and symptomatic forms of frontotemporal lobar degeneration.

The Advancement in Research and Treatment in frontotemporal lobar degeneration (ARTFL) and the Longitudinal Evaluation of Familial Frontotemporal lobar degeneration subjects (LEFFTDS). A research consortium involving 23 sites in North America.

The FTD Disorders registry (FTDDR) managed by the Association for Frontotemporal degeneration in partnership with the Bluefield Project.

4) Conclusion

Frontotemporal dementia is common dementia, particularly in individuals younger than 65 years

Frontotemporal dementia and its related disorders are a spectrum of fatal neurodegenerative diseases with a finite number of pathophysiologies that are rapidly being elucidated.

This is particularly true for the genetic forms of frontotemporal dementia and for frontotemporal dementia with Tau pathology for which several targets have been identified and a number of therapies have been /are being tested in clinical trials.

However, several challenges must be overcome to recruit homogenous patient cohorts and ensure that appropriate biomarkers and clinical endpoints are used so that clinical trials produce meaningful results.

5) Resources :

Frontotemporal disorders. Information for patients, families and caregivers. National Institute of Health

Frontotemporal Dementia Mayo Clinic

The Association for Frontotemporal Degeneration

https://www.ninds.nih.gov/Disorders/All-Disorders/Frontotemporal-Dementia-Information-Page

Frontotemporal dementia-Alzheimer Society Canada

FTD Disorders Registry

6) References :

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