Teaching Course 14

Neuropsychiatric and behavioural symptoms in neurodegenerative diseases - Level 1

Management of neuropsychiatric symptoms in frontotemporal dementia

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Recognizing FTD:
A correct diagnosis is the first prerequisite for adequate clinical management. The first critical step is to recognize the disease and not to confound it with more common diseases such as Alzheimer’s disease or with psychiatric diagnoses. It still happens that a case with a typical phenotype of frontotemporal dementia behavioral variant (FTD bv) receives a diagnosis of Alzheimer’s disease even by neurologists, to be corrected thereafter by the family members who are looking up the disease characteristics via online educational material. It is therefore important to put clinical procedures in place to reduce the number of cases with frontotemporal dementia who are misdiagnosed. Three measures appear of use: During the outpatient visit to see patient and caregiver first together and then separately, secondly, to be aware of the consensus criteria and apply them clinically, thirdly, the use of scales developed to elicit symptoms that are indicative of FTD rather than AD.

Good quality care for FTD requires the ability to listen to the caregiver and his/her report about the daily observations in a one-to-one conversation. A conversation with the family member separately is of great value to get a full and open account of the type of changes that the family is noticing.
In clinical-neurological practice, the detection of frontotemporal dementia is greatly helped by the use of the Rascovsky et al (2011) consensus criteria for the diagnosis of frontotemporal dementia behavioral variant. These criteria help the neurologist to get a handle on the complex and often fundamental alterations in behavior and personality in typical FTD. Each of the items should be considered as a cluster of symptoms, which in itself may consist of several subclusters which may be neuroanatomically dissociable or not. The different items are a good start for organizing the history taking with the family member. According to the consensus criteria the diagnosis of possible FTD bv requires the presence of at least 3 of the following symptoms:

1. **Apathy**: Apathy is a symptom cluster that consists of several subclusters. One of these subclusters refers to the lack of interest, e.g. loss of interest in longstanding hobbies or loss of interest in what happens within the family or a narrowing of interest to just one or two topics. Another subcluster refers to the increase in threshold before the patient initiates an act, even if he/she agrees to it voluntarily. In itself, apathy is not a disease-specific symptom cluster and as will be clear during this course, also occurs in many other neurodegenerative diseases.

2. **Disinhibition**: Like apathy, disinhibition is a cluster of symptoms. We all constantly apply implicitly or explicitly social rules of how we behave toward others and how we do not behave. One of the subclusters covered by disinhibition is the unknowing transgression of these rules. This may be manifest through excessive familiarity towards strangers (hugging, confidential talk, ..), inappropriate engagement with children the patient does not know, loud racist remarks, sudden
and unexpected sexual language, use of taboo words, aggressive behavior during traffic, shoplifting etc. Another subcluster relates to changes in decision making with altered risk assessment. This may lead to financial debts with excessive and impulsive expenditures, transgressive sexual proposals, risks during car driving, ... and may lead to involvement of police and judicial procedures, most frequently during the delay between symptom onset and an accurate diagnosis of FTD.

3. **Changes in eating behavior:** One of the symptom subclusters covered by this item relates to how the patient is behaving at the table: Change of the speed of eating, change of the amount of food that is held intraorally prior to deglutition, loss of table manners, such as taking food from somebody else’s plate, or starting to eat while others are still not sitting at the table. Another subcluster relates to what and how much the patient eats. Often, the caloric intake is increased with craving for calory-rich drinks such as excessive amounts of softdrinks or of high-caloric sugar containing food ingredients such as pastry, cookies, or chocolate. There may be addictive behavior for nicotine and alcohol. The food ingredients the patient wants may become narrowed down to one particular category, e.g. a particular type of soup. A third type of change relates to the perception of what is edible: Patients with FTD bv in a more advanced stage may have a tendency to put inedible objects into their mouth. Finally, there may be a loss of aversion for drinks that are still too hot, eg hot soup.

4. **Loss of empathy and sympathy:** Patients with FTD bv are less responsive to the expressions of affect such as sadness. The family may report that the patient reacts indifferently to expressions of sadness of the partner. Patients with FTD may also attribute less importance to
the problems and concerns of close relatives than before, eg serious medical problems.

5. **Repetitive, ritualistic or obsessive behaviors**: This is a very large symptom cluster that encompasses a wide variety of different symptoms. Patients with FTD bv may be much more rigorous and lack flexibility to adapt their behaviors based on rational arguments. Another symptom cluster relates to repetitive simple motor behaviors such as sniffing, rubbing the thigh, coughing or rhythmic movements of a leg. Repetitive behaviors may also be cognitive in nature, e.g. obsessive counting behaviors, for instance of tiles or of damage along the highway, or stereotyped overlearned verbal behavior.

6. **Executive dysfunction**: This is probably the least specific criterion. It may refer to abnormal scores on neuropsychological tests, such as the Wisconsin Card Sorting test, and to the problems with planning and organization. The executive dysfunction also implies that patients with FTD bv who are living alone most often need to be institutionalized relatively soon in the disease course because they lack the basic skills to organize their household if not supervised.

The diagnosis of possible FTD bv also requires the absence of some exclusionary features, such as problems with visuoconstructional apraxia and amnestic deficits early in the disease. This exclusionary criterion of the consensus guidelines will be discussed later.

A diagnosis of probable FTD bv requires the presence of hypometabolism or atrophy on imaging.
Consensus criteria require further validation. One validation approach would consist of prospective application of the criteria to a sufficiently wide variety of patients in a relatively early stage and validate the sensitivity and specificity of the criteria against the neuropathological diagnosis. Another approach is to evaluate the criteria in patients with proven genetic causal mutations. Based on the latter type of studies it is clear that the consensus criteria do not adequately capture the clinical presentation of a substantial number of patients with definite FTLD. This will be illustrated during the teaching course for TBK1 mutations and for c9orf72 expansions by means of case studies. Several elements of the clinical course deviate from what one would expect based on the consensus criteria. Most notably, a classical amnestic syndrome that is indistinguishable from that seen in typical AD can be the initial manifestation of FTLD for several years (van Mossevelde et al., 2015). Secondly, psychosis with obsessive features are relatively common in FTLD due to c9orf72 expansions and this also differs from what the consensus criteria would capture (Ducharme et al., 2017). Third, FDG PET can be normal even far in the course of patients with FTD bv due to c9orf72 expansions. Overall, the sensitivity of FDG PET for detecting FTLD is estimated to be around 80%. Finally, from these genetic studies and other cohort studies it has become clear that a very substantial portion of FTLD patients (maybe as high as one third) are older than 65 years at symptom onset.

While the typical full-blown phenotype of FTD bv should always be recognized by a neurologist, the disease can sometimes manifest itself in more subtle manners and can be confounded with Alzheimer’s disease even in very experienced academic centres. For proper patient management and follow-up it is therefore important to increase the
sensitivity for detecting FTLD. In the teaching course we will present three approaches that may be very helpful in that respect. First, we advise the frequent use of the Frontotemporal Dementia Rating scale. This scale is an unbiased series of questions that are very close to the clinical reality and may help the clinician to uncover aspects of the clinical manifestation that may otherwise remain hidden. Second, it is very useful to see patient and family together and also separately. In a survey of family members of patients with early-onset dementia, the possibility to see the physician each separately was one of the most appreciated clinical care aspects. Third, a more systematic use of amyloid biomarkers may be very helpful in detecting the amyloid-negative cases. This is the topic of large-scale prospective ongoing trials in the EU as well as in the US.

Several scales have been developed for eliciting conversation about symptoms suggestive of FTD. The Frontotemporal Dementia Rating scale http://www.ftdrg.org/ace-r-download/frontotemporal-dementia-rating-scale-frs-download/, will be discussed in detail during the course and is particularly useful for the clinician as it remains very close to the type of concrete examples that come up during history taking in FTD.

Potential role of drug treatment in FTD

There is no class I evidence regarding any drug in FTD bv. Here we discuss some of the drugs that could be considered and have been used and provide expert opinions about their role in managing behavioral problems in FTD.

• **Trazodone:** Trazodone was shown to be beneficial in a small trial (Lebert et al. 2004) in a group of 26 FTD cases. Doses to be used range from 50 mg od up to 150 mg three times a day. Trazodone may temper
some of the difficult behavioral symptoms. The Neuropsychiatry Inventory Domains that showed a significant benefit were irritability, agitation, depressive symptoms and eating disorders. In 10 patients the NPI score improved by 50%. The main side effects in this population are orthostatic hypotension, increased fall risk, and sleepiness.

- **Memantin:** A randomized placebo-controlled trial in 81 FTD bv or Semantic Dementia cases (Boxer et al, 2013) with memantine did not yield a significant benefit on the NPI or the Clinical Global Impression of Change scale. We therefore do not recommend the use of memantine in FTLD.

- **Neuroleptics:** Avoid the use of neuroleptics as much as possible. Prolonged use of neuroleptics can have a severe negative effects in FTD. Extrapyramidal side effects may be very pronounced and render the patient wheelchair bound and substantially increase the risk of falls. It may lead to hypophonic dysarthria and affect speech and eating with risk of aspiration pneumonia. Neuroleptics may increase apathy and somnolence and may increase restlessness, up to a point where the patient can hardly sit on a chair for more than a few minutes (akathisia). The frequent problem of weight gain may be further exaggerated by adding a neuroleptic such as quetiapine. If a neuroleptic is necessary, the patient must first receive a clinical neurological examination to detect any pre-existent extrapyramidal signs, an ECG to evaluate the QTc interval, and measurement of weight and blood pressure measurement supine and standing.

Sometimes, for the repetitive and the obsessive behaviors, olanzapine or risperidone in a low dose can have a mildly positive effect but this should be restricted to a minimum. Towards the family, it should be emphasized
that the drastic behavioral and personality changes associated with FTD cannot be solved with neuroleptic drug therapy and that these can aggravate some of the symptoms substantially.

- Low-dose benzodiazepines can in our experience sometimes have a mildly positive effect for persistent somatic hypochondric complaints and for nighttime restlessness.

- Selective serotonin reuptake inhibitors: In analogy with the treatment of obsessive compulsive disorder, SSRI has been sometimes used in an effort to reduce the obsessive behaviors.

- The use of cholinesterase inhibitors is relatively contraindicated given the potential side effects such as gastrointestinal complaints and urinary incontinence and the lack of efficacy. According to case reports, they may also augment agitation.

**Adapting the environment to the patient**

Instructions and efforts to change the patient’s behavior are most often fruitless and frustrating for the patient and the caregiver. There is a very important role for psychoeducation. A physician or a paramedical team member should be available during the working hours to be contacted in case of need. If necessary, an integrated FTLD clinical path should also include the possibility to hospitalize the patient on an appropriate ward in case of violent or totally disruptive behavior.

According to one of the basic rules in FTLD management, the environment should be adapted to the patient as much as possible. Deviant behavior should be tolerated rather than trying to correct it. Efforts to make the patient’s behavior conform to the norms through instruction are most
often fruitless given the lack of mental flexibility and lack adaptive learning typical for this disease.

Caregivers can sometimes be remarkably inventive in how they put some aspects of the behavioral abnormalities to use in order to steer behavior. For instance, in order to stimulate the patient to walk, the spouse may promise a rewarding food intake in a restaurant at the end destination of the walk, to motivate the patient.

It may be useful to explain to the caregiver that some of the disruptive behaviors are only present during a given phase in the disease and may subsequently get better as the disease progresses, and e.g. apathy becomes more pronounced.

**Approach to specific behavioral problems**

- **Apathy:** For the partner apathy is burdensome. Initially the partner may attempt to go against the lack of initiative. This often originates from a concern that lack of activity will have a negative effect on the disease progression but often leads to frustration. In principle, apathy is not associated with any suffering from the side of the patient and the general advice is to invite the patient to join activities but not waste energy trying to remediate the apathy.

- **Repetitive behavior:** this can be very enervating to the caregiver and lead the caregiver to loose control, eliciting aggression from the patient in turn. It is virtually impossible to suppress the repetitive motor behaviors except at the cost of high doses with negative side effects.
- **Restlessness:** We also advice not to try to suppress this type of behavior by medication or by behavioral interventions. From a positive side, it could be regarded as a form of physical activity that may help maintain physical fitness and contribute to a good night rest.

- **Harmful or risk behaviors:** It is important to discuss openly behaviors that may cause the patient harm such as shoplifting or incurring debts from expenses made impulsively or online so that preventive measures can be taken.

- **Eating behavior:** At initial presentation and follow-up the weight of the patient should be monitored and the attention of the caregiver should be drawn to the importance of keeping the weight gain within an acceptable range. The increased caloric intake through intake of soft drinks, pastry or sugary ingredients can only be controlled by restricting the access to these ingredients, eg by hiding them out of sight or by not having them in house in any large quantities. Alcohol overconsumption can occur and the only remedy is to try to reduce the amount of alcoholic drinks to which the patient has access. Nicotine addiction is also rather frequent. Again, some caregivers are inventive in how they deal with this: They have fixed hours of the day when the patient can come and ask for a pre-set number of cigarettes and this type of directive rules can often be learnt and obeyed very well by the patient.

- **Agression:** One of the behavioral symptoms in FTD that is considered as most intrusive and painful for the caregiver is physical aggression. This may lead to institutionalization and may require physical restraints. In these extreme circumstances the temporary use of high-dose neuroleptics can sometimes be unavoidable.
Underlying neuroanatomical networks and cognitive models

The processes that are dysfunctional and lead to the personality and behavioral manifestations of FTD bv are many and can certainly not be reduced to one or a few systems. The most relevant cognitive models from cognitive and behavioral neuroscience relate to the learning of stimulus-response associations and the role of prefrontal damage, decision making models, and models of perception of emotions.

For many of the behaviors, the underlying anatomical network remains to be fully delineated. Two influential models for the behavioral changes in FTD will be discussed during the course. Seeley et al (2009) has implicated mainly the salience network in FTD, which consists of the anterior insula bilaterally and the anterior cingulate. According to a separate model (Bickart et al., 2014), the key structure is the amygdala which is at the crossroad of three networks that are involved in FTD: the perceptual network, the affiliative network and the aversive network. The amygdala contains more than 20 nuclei. These three networks involve different amygdalar nuclei. The perceptual network mainly relates to the processing of emotions and involves the medial and basolateral nuclei as well as the anterior portion of the ventral occipitotemporal pathway. The affiliative network mainly involves medial amygdalar nuclei and nodes from the ventral striatum. The aversive network mainly overlaps with the pain network and involves the dorsal amygdala as well as the posterior part of the anterior cingulate as well as the insula. According to this model the complex behavioral changes in FTLD result from damage to these three different networks.
Conclusion:

Management and care for patients with FTD and their families is founded on attentive listening to what the caregivers report so that their needs can be addressed. Among the basic rules are to try to adapt the environment to the patient rather than the inverse and to provide contact coordinates within the clinical team in case of need when violent or excessively disruptive behaviors make living at home temporarily impossible. There is only a limited role for drug treatment and no class I evidence for any efficacious drug.
Selection of key references


- Van Mossevelde, S.; et al. Clinical features of TBK1 carriers compared with C9orf72, GRN and non-mutation carriers in a Belgian cohort. *Brain*, 2016, 139, 452-467