Frontotemporal Dementia and ALS in daily Practice: Red Flags

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ALS to FTD

ALS-motor
50%

ALSSci - cognitive impairment and/or
ALSbi – behavioural impairment
35%

GGGGGCC repeat expansion in the \textit{C9orf72} gene in
ALS and in FTD

TAR DNA binding protein, TDP-43 most common
pathology in ALS and also in FTD

Frontotemporal dementia (FTD) <15%

\textit{Behavioural variant: bvFTD}
\textit{Characterised by Personality Change}
### International consensus criteria for behavioural variant FTD (FTDC)

**II. Possible bvFTD**

Three of the following behavioural/cognitive symptoms (A–F) must be present to meet criteria. Ascertainment requires that symptoms be persistent or recurrent, rather than single or rare events.

A. **Early*** behavioural disinhibition [one of the following symptoms (A.1–A.3) must be present]:
   - A.1. Socially inappropriate behaviour
   - A.2. Loss of manners or decorum
   - A.3. Impulsive, rash or careless actions

B. Early apathy or inertia [one of the following symptoms (B.1–B.2) must be present]:
   - B.1. Apathy
   - B.2. Inertia

C. Early loss of sympathy or empathy [one of the following symptoms (C.1–C.2) must be present]:
   - C.1. Diminished response to other people’s needs and feelings
   - C.2. Diminished social interest, interrelatedness or personal warmth

D. Early perseverative, stereotyped or compulsive/ritualistic behaviour [one of the following symptoms (D.1–D.3) must be present]:
   - D.1. Simple repetitive movements
   - D.2. Complex, compulsive or ritualistic behaviours
   - D.3. Stereotypy of speech

E. Hyperorality and dietary changes [one of the following symptoms (E.1–E.3) must be present]:
   - E.1. Altered food preferences
   - E.2. Binge eating, increased consumption of alcohol or cigarettes
   - E.3. Oral exploration or consumption of inedible objects

F. Neuropsychological profile: executive/generation deficits with relative sparing of memory and visuospatial functions [all of the following symptoms (F.1–F.3) must be present]:
   - F.1. Deficits in executive tasks
   - F.2. Relative sparing of episodic memory
   - F.3. Relative sparing of visuospatial skills

**III. Probable bvFTD**

All of the following symptoms (A–C) must be present to meet criteria.

A. Meets criteria for possible bvFTD

B. Exhibits significant functional decline (by caregiver report or as evidenced by Clinical Dementia Rating Scale or Functional Activities Questionnaire scores)

C. Imaging results consistent with bvFTD [one of the following (C.1–C.2) must be present]:
   - C.1. Frontal and/or anterior temporal atrophy on MRI or CT
   - C.2. Frontal and/or anterior temporal hypoperfusion or hypometabolism on PET or SPECT

**IV. Behavioural variant FTD with definite FTLD Pathology**

Criterion A and either criterion B or C must be present to meet criteria.

A. Meets criteria for possible or probable bvFTD

B. Histopathological evidence of FTLD on biopsy or at post-mortem

C. Presence of a known pathogenic mutation
Partner’s perspective

“My own GP has told me that ALS just affects the limbs and NOT the brain functions. I have to disagree as in one year of my late husbands life I saw the change of a caring conscientious family man into an uncaring/unsympathetic, confused, aggressive person. That none of his family or friends recognised. A professional man that did the most bizarre things that were totally out of character.

Even colleagues had noticed that he had gone from a very efficient team leader to a 'couldn't care less attitude' even before he was diagnosed. ... He became unrecognisable like a stranger even though we had been married 22 years.”

“The professionals he saw did not in their appointments see the man he had become”
Apathy: Dimensional Apathy Scale

Radakovic & Abrahams
https://das.psy.ed.ac.uk/

Executive Apathy
I can’t seem to finish things

Initiation Apathy
I can’t think of any new ideas

Emotional Apathy
I am not bothered, I don’t care

Is it Apathy or Depression?:
Apathy neutral emotions/thoughts, Depression negative emotions/thoughts
Apathy in bvFTD without ALS
Psychiatric symptoms in ALS

- Depression and anxiety are common in people with ALS and their family members.
- ALS family members compared with healthy controls report higher levels of current anxiety and OCD, and are more likely to report a lifetime episode of:
  - Psychosis
  - Alcohol use
  - Mania
  - Self-harming behaviour

Current and/or history of psychiatric symptoms are associated with poorer cognition and the presence of behaviour changes:

**ALS Proband**
- Depression
- Anxiety
- ADHD
- Psychosis
- Mania

**Family members**
- Anxiety
- ADHD
- Impulsivity
- Autism

Do not dismiss psychiatric symptoms.
Planning, organising, problem solving, thinking of new ideas and decision making

The most striking and consistently reported deficit: **Letter Fluency** Ship, Shore, Snake, Silly, Send, Silver, Sonnet, Sun...

Verbal Fluency Index (Vfi):
Average time to ‘think’ of each word independent of motor disability

\[ V_{fi} = \frac{\text{time allowed for test} - \text{time to copy word}}{\text{number of words}} \]
Letter fluency & Functional Brain Imaging

Word Generation
Impaired Activation in MNDi group compared with Controls
(p<0.001)

A for Alpha

“apple” “ankle” “ant”

PET (H$_2^{15}$O) and fMRI dorsolateral prefrontal cortex and Anterior Cingulate dysfunction during letter fluency
Is the cognitive deficit in ALS due to slowed processing speed or executive dysfunction (multi-tasking)?

Processing Speed Task - Visual Inspection Time (VIT):

“Right/Left”

Dual Task Procedure

Present Numbers

“2 6 4 7 1 9”

Recall Numbers

“2 6 4 7 1 9”

Visual Inspection Task
ALS patients show dual task (executive) impairment and normal information processing speed.

Uncinate and Cingulate integrity affected in ALS.

Dual task and verbal fluency correlates with DTI indices for middle and superior frontal lobe white matter.
11/25 (44%) of ALS patients tested who displayed dysarthria showed language difficulties with in particular spelling problems. Philipa Rewaj and Thomas Bak

Look for communication problems which are not due to physical dysarthria
Evidence of Social Understanding Impairment in Patients with Amyotrophic Lateral Sclerosis

Marco Cavallo, Mauro Adenzato, Sarah E. MacPherson, Gillian Karwig, Ivan Enrici, Sharon Abrahams

Social Cognition Deficit in ALS
Deficit in understanding social but not non-social situations
36% of ALS impaired in simple theory of mind test
Increased egocentric responses in ALS.
Look for difficulties in social behaviour
How can we assess quickly and efficiently?

*The Edinburgh Cognitive and Behavioural ALS Screen (ECAS) in ALS*
Edinburgh Cognitive and Behavioural ALS Screen (ECAS)

Brief: 20 min assessment for ALS health professional
Designed for physical disability (written or spoken responses)

For health care professionals supervised by a neuropsychologist.

All people with ALS in Scotland are routinely offered to undertake this brief assessment. All nurses have been trained to undertake this assessment.

The results are incorporated into routine clinical care to help with management.
Edinburgh Cognitive and Behavioural ALS Screen (ECAS)

The ECAS is a brief multidomain assessment originally designed for people with Amyotrophic Lateral Sclerosis (ALS/Motor Neurone Disease) but is also useful in other neurodegenerative disorders.

It makes cognitive assessment fast and accessible and can be undertaken by a health care professional in the clinic or in a patient's home.

The ECAS was designed by Sharon Abrahams, Thomas Bak and Judy Newton.
ECAS
Anterior functions/ALS-Specific: language, executive and fluency)

Posterior functions/
ALS Non-Specific: memory and visuospatial

Language
Naming
Comprehension
Spelling
ECAS

- Letter Fluency
  Free Fluency: S Words
  Sail, Send, Sorry

  Fixed Fluency: T 4L Words
  That, Talk, Tank

Verbal Fluency Index
ECAS

- Executive Functions
- Reverse Digits
- Alternation
- Inhibitory Sentence Completion
- Social Cognition
ECAS

- **Executive Functions**
- Reverse Digits
- Alternation
- Inhibitory Sentence Completion
- Social Cognition

**SOCIAL COGNITION – Part B**

Say: You are going to see some pictures, one in each corner of a box. You have to choose which picture does the task like best. Either point to or say which picture does the task like best. Please respond as quickly as possible. Circle participant’s choice. Correct items = 2 points, error = 1 point, egocentric error = 0 points.

<table>
<thead>
<tr>
<th>Score</th>
<th>0-12</th>
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<tbody>
<tr>
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<td></td>
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</table>
ECAS

- Memory
  Story Recall
  Immediate
  Delayed Retention (%)
  Recognition

MEMORY – Immediate recall

Say: ‘I am going to read you a short story. Please listen carefully. When I am finished, say or write as much as you can remember’. Score 1 point for each (either entire or part of) underlined section recalled.

Last Sunday, the annual litter collection took place in Primrose Woods. Forty-two people joined in to remove old bicycles and shopping trolleys. Mr Douglas Watt from the woodland project told local reporters that he was very impressed and especially proud of the 17 children who came along.

MEMORY – Delayed Recognition

If all items recalled, skip and score 4. Otherwise ask questions below.

Say: ‘Let’s see if you can remember anything more about that story. I will ask you some questions, please tell me if they are true or false’.

Circle responses (true or false) and score 1 point for each item recognised in this section. Use table below to calculate score.

<table>
<thead>
<tr>
<th>Question</th>
<th>T</th>
<th>F</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was the story about an event that occurred last Saturday?</td>
<td>T</td>
<td>F</td>
<td>1</td>
</tr>
<tr>
<td>Was the event the annual litter collection?</td>
<td>T</td>
<td>F</td>
<td>1</td>
</tr>
<tr>
<td>Did this take place in Primrose Woods?</td>
<td>T</td>
<td>F</td>
<td>1</td>
</tr>
<tr>
<td>Did they remove old drink cans and sweet wrappers?</td>
<td>T</td>
<td>F</td>
<td>1</td>
</tr>
<tr>
<td>Was the man in the story called Mr Watt?</td>
<td>T</td>
<td>F</td>
<td>1</td>
</tr>
<tr>
<td>Was his first name “Thomas”?</td>
<td>T</td>
<td>F</td>
<td>1</td>
</tr>
<tr>
<td>Was he from the local council?</td>
<td>T</td>
<td>F</td>
<td>1</td>
</tr>
<tr>
<td>Was he especially proud of the children for coming along?</td>
<td>T</td>
<td>F</td>
<td>1</td>
</tr>
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</table>

Recognition to recognition score table

<table>
<thead>
<tr>
<th>Number of correct answers</th>
<th>Converted Score</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
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<tr>
<td>1</td>
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<tr>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>
ECAS

- **Visuospatial**
  - Dot Counting
  - Cube Counting
  - Number Location
<table>
<thead>
<tr>
<th></th>
<th>Frequency of Deficit</th>
<th>% Abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALS-Specific</td>
<td>28</td>
<td>35.9%</td>
</tr>
<tr>
<td>ALS Non-Specific</td>
<td>6</td>
<td>7.7%</td>
</tr>
<tr>
<td>ECAS Total</td>
<td>28</td>
<td>35.9%</td>
</tr>
</tbody>
</table>

Scores 85% to 92% sensitive and 85% specific against gold standard full neuropsychological assessment
35 carer interviews, 51% of patients with behaviour change (1 or more domains)
ALS-specific cognitive and behavior changes associated with advancing disease stage in ALS

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ECAS sensitive to bvFTD without ALS and AD

ECAS vs ACE-III in bvFTD
Anterior Score (executive, language, fluency) 94% sensitive 92% specific

ECAS vs ACE-III in AD
Posterior Score (memory and visuospatial) 97% sensitive 96% specific
Mental capacity in ALS

- The ability to make a specific decision at a specific time.
- Capacity assumed unless demonstrated otherwise.
- Should I join this clinical trial?
- Should I consent to having a gastrostomy when/if the time comes?
- Should I consent to genetic testing

Cognitive assessment (ECAS) can help to inform this process, but cannot tell you if someone has capacity to make a decision. You need to refer for a capacity assessment to a Psychiatrist/Psychologist.
Video case

Person with bvFTD
Poll

1. Did the woman in the video show...
   - Cognitive and Behaviour change
   - Cognitive change only
   - Behavioural change only
   - None of the above
   - We can’t tell

2. Did the daughter’s description of her mothers behaviour include...
   - Disinhibition
   - Loss of sympathy/empathy
   - Apathy
   - Perseverative behaviour
   - All of the above
Summary of red flags

- ALS is not only a disease of the motor system
- ‘Mother knows best’, do a separate interview with someone who knows them well to check for behaviour change
- Be careful to consider other causes of behaviour abnormalities, e.g. marital discord...
- Do not dismiss psychiatric symptoms
- Take into account physical disability in the assessment
- Look for problems with attention, decision making and also language and social behaviour
- Use an appropriate assessment supervised by a neuropsychologist
- Remember some people will show behaviour change but unimpaired cognition, check both
- If someone is cognitively impaired does not mean that do not have mental capacity... Capacity assessments must be undertaken in full.
Thank you to
Research Team: Debbie Gray, Caroline McHutchison, Ratko Radakovic, Lewis Pettitt.
Thomas Bak

and all the people with ALS and their families who have participated in our research