Motor Neuron Disease: Recent Advances

Dr. Muhammad Rafiq MRCP (UK), PhD
Consultant Neurologist
Co Director Norfolk MND care and Research Centre

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Motor Neuron Disease

- Third commonest neurological disease of later life
- First described in 1886
- Lifetime risk 1:400, prevalence of 5-7 per 100,000
- Progressive loss of motor neurons and weakness of limb, speech & swallowing and respiratory muscles
MND - clinically, genetically, pathologically and prognostically a heterogeneous condition
Genetics of MND

- Sporadic (SALS) ~ 95%
- Familial (FALS) ~ 5% of cases

- 
  C9ORF72, SOD1 and TDP-43 gene mutations are the most important genetic causes of familial MND

- However, genetic factors also likely to play a role in apparently sporadic disease
Risk Factors associated with the development of Sporadic MND

- Age
- Gender
- Genetic factors

Potential environmental risk factors remain unproven *eg*:

- Athleticism / physical exercise
- Trauma
- Toxins *eg* solvents, cyanobacteria
- Smoking
- Electric shock
- Occupation *eg* military, airline pilot, professional football
MND is a TDP43-proteinopathy in most but not all cases.
Two approaches for improved neuroprotection:
1. Drugs which will hit multiple aspects of the pathobiology
2. Gene therapy to modify the expression of the rogue gene
Gene therapy for neuroprotection in motor neuron diseases

- Gene over-expression, e.g. trophic factors, anti-oxidants
- Gene silencing (RNA interference)
- Gene replacement (SMN gene)
- New developments in viral vector technology

Strong expression of LentiVector encoding LacZ in muscle and spinal motor neurons of SOD1^{G93A} mice

Mimoun Azzouz et al., Nature 2004
Biogen SOD1 Antisense-Oligonucleotide Phase 1 Trial

An antisense oligonucleotide (ASO) against SOD1 delivered intrathecally for patients with SOD1 familial amyotrophic lateral sclerosis: a phase 1, randomised, first-in-man study

Timothy M Miller et al,

- ASO - short synthetic nucleic acid chemically modified to increase stability in biological fluids and potency of binding to mRNA target.

- Bind to specific target mRNA and promotes its degradation by activation of the nuclear enzyme RNaseH. Estimated half life 28 days.

- Administered intrathecally in increasing doses to 4 cohorts of 8 patients.

- No toxicity or safety concerns.

- Possibility of using CSF SOD1 levels as a pharmacodynamic marker.

- New ASO Phase 1 trial in set-up in the UK with enrollment started in Spring 2016.
Stem cell therapy in MND

• Several types of stem cells have been studied in animal models to modify disease pathophysiology:

1. **Embryonic neural stem cells** transplanted in cervical and lumbar segments of spinal cord could differentiate into neurons and form synaptic connections with muscles.

2. **Mesenchymal stromal cells** offer trophic support to motor neurones by delivering neurotrophic, anti-inflammatory, and immunomodulatory molecules.

3. **Induced pluripotent stem cells** can differentiate into astrocytes and motor neurones, provide protective factors and even replace injured cells.
WHILE WE WAIT......
for improved neuroprotective treatments

Much can be done to help well being, improve survival and quality of life by careful symptom management
Dose-ranging study of riluzole in amyotrophic lateral sclerosis

*Lancet* 347:1425-1431; 1996

**Efficacy results (2)**

**Study 301: Kaplan-Meier survival curves for riluzole, 100 mg/day, and placebo**
The importance of good multidisciplinary symptomatic care

- Survival of all MND patients from symptom onset who attended a general neurology clinic or the multidisciplinary clinic (months).

- Attending the multidisciplinary clinic improves average survival of the patients by 9 months and reduces overall mortality at 1 year from diagnosis by 28%.

Effect is independent of gastrostomy, non-invasive ventilation, Riluzole
Weakness of the Respiratory Muscles in MND

- Like any other skeletal muscle, respiratory muscles are also affected in motor neuron disease (MND).

- The major consequences of respiratory muscle weakness include:
  - Respiratory failure
  - Inability to cough effectively

- Respiratory insufficiency is the major cause of morbidity and mortality in MND.

- Supporting respiratory function and preventing chest infections may prolong survival and improve quality of life.
Randomised trial of non-invasive ventilation in MND

Improvement in life expectancy post randomisation

NIV

Controls

p = 0.006

Days

0.00
0.25
0.50
0.75
1.00

0
200
400
600
800

SC Bourke, T Williams, PJ Shaw, GJ Gibson
Lancet Neurology 2006

NICE GUIDELINE 2010

APPROVED
A randomised controlled trial evaluating NeuRx/4 Diaphragm Pacing in patients with respiratory muscle weakness due to Motor Neuron Disease or Amyotrophic Lateral Sclerosis.
HR 2.27 (95% CI 1.22 to 4.25; p=0.01)

Median survival from randomisation: NIV + DPS 11.1 months
NIV alone 22.8 months

DIPALS STUDY group Collaborators Lancet Neurology 2015
Effects of cough augmentation on morbidity, quality of life and survival in patients with motor neuron disease using non-invasive ventilation: a randomized clinical trial

ISRCTN 43911973

Mechanical in-exsufflator
Cost £4000

Manual insufflator
Cost £16

Rafiq M, Proctor A Shaw PJ ALS & FTD 2015
GASTROSTOMY IN PATIENTS WITH MOTOR NEURONE DISEASE: A PROSPECTIVE COHORT STUDY (PROGAS)
<table>
<thead>
<tr>
<th>Benefit</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stabilise nutrition &amp; hydration</td>
<td>87.2%</td>
</tr>
<tr>
<td>Ease feeding difficulties</td>
<td>78.6%</td>
</tr>
<tr>
<td>Reduce choking risk</td>
<td>77.4%</td>
</tr>
<tr>
<td>Improved quality of life</td>
<td>77.4%</td>
</tr>
<tr>
<td>Alternative medication route</td>
<td>70.3%</td>
</tr>
<tr>
<td>Reduce aspiration risk</td>
<td>65.0%</td>
</tr>
<tr>
<td>Reduce pneumonia risk</td>
<td>65.0%</td>
</tr>
<tr>
<td>Prolong survival</td>
<td>47.8%</td>
</tr>
<tr>
<td>Reduce carer burden</td>
<td>44.5%</td>
</tr>
</tbody>
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Neck Muscle Weakness:
A common and uncomfortable problem in MND
Head Up Project

- User group sessions identified current problems and importantly what is actually required by patients:
  - Support allows movement
  - Adaption to patients needs
    - Customise to each patient
    - Customise over time
  - Artificial support should replace type of support originally provided by weakened muscles

- Collaboration between Neurologists, MDT team (nurses & physiotherapists) Patients, Carers, Bioengineers, Materials Scientists, Fashion Designers, Commercial companies
Nutritional Interventions

- **Motor Neuron Disease** is a hyper-metabolic state.
- Some evidence of benefit of high protein/high lipid diet.
- **Post GAS**
- **High CALS**
Norfolk MND Care Centre

- **Directors:**
  - Dr. David Dick
  - Dr. Muhammad Rafiq

- **Care Co-ordinator:**
  - Mrs. Helen Copsey

- **Respiratory Consultants**
  - Dr. Phillipe Grunstein
  - Dr. Prasana Sankaran

- **Gastroenterology Consultants**
  - Prof. A Forbes
  - Dr. Dana Ismail
Key Aspirations

- To be accessible to all patients with MND within Norfolk
- Rapid access - all suspected patients seen within 2-3 weeks of referral
- Provide a multi-disciplinary care in a co-ordinated fashion which is least time consuming for patients
- Having respiratory assessments within the Neurology clinic
- Early intervention with Gastrostomy
- All patients have an opportunity to take part in research
Acknowledgements

ALL OF YOU

mnda
motor neurone disease association