

MANUAL FOR NEWCASTLE MITOCHONDRIAL DISEASE ADULT SCALE (NMDAS)

Introduction

The NMDAS has been introduced to allow evaluation of the progression of mitochondrial disease in adult patients over 16 years. The Newcastle Mitochondrial Disease Paediatric Scale (NMDPS) provides a similar assessment tool for paediatric patients. Repeated administration of the scale provides a quantitative assessment in the longitudinal follow up of patients with mitochondrial disease of any genetic cause. The use of this rating scale will standardise patient assessment and ensure more accurate data collection to aid our understanding of the natural history of mitochondrial disease. It is predicted that the scale will also prove to be an invaluable tool for future clinical assessment of proposed treatments.

The rating scale encompasses all aspects of mitochondrial disease by exploring several domains: Current Function; System Specific Involvement; Current Clinical Assessment and Quality of Life. We advise that the scale should be administered at either six or twelve month intervals by clinicians with experience in the care of patients with mitochondrial disease.

This rating scale has been validated by the Newcastle Mitochondrial Disease Research Group on two separate occasions through the administration of the scale by 4 clinicians to 16 and 15 patients respectively. The scale demonstrated good to excellent agreement between raters for individual domain scores and the overall disease score. However, this agreement can only be ensured if all users of the scale adhere closely to the instructions given in this manual. Individual interpretation of the questions will alter the scores assigned and consequently reduce the consistency and reliability of the data collected. This instruction manual should be fairly self explanatory but if any points are unclear please contact Dr Andrew Schaefer on andrew.schaefer@nuth.nhs.uk

Section I: Current Function

General points

This section rates current function **according to the patient** and is **not based upon the physician's own judgement**. The caregiver may be interviewed if the patient's cognitive function is impaired as patients become increasingly difficult to interview (leading to a reduced inter-rater reliability) as cognitive impairment increases. Hence a score is assigned according to the patient's / carer's opinion of the patient's functional abilities, and is independent of the clinician's knowledge of the patient and the clinical signs. Each enquiry should take into account the situation for the **preceding four week period** only.

We believe the method of questioning the patient is important. To illustrate the proposed method, we consider the first question in this section:

1. **Vision** with usual glasses or contact lenses
 0. Normal.
 1. No functional impairment but aware of worsened acuities.
 2. Mild - difficulty with small print or text on television.
 3. Moderate - difficulty outside the home (eg bus numbers, road signs or shopping).
 4. Severe - difficulty recognising faces.
 5. Unable to navigate without help (eg carer, dog, cane).

We believe that it is important to ask direct questions about visual function rather than vague questions such as "any problems with vision?", as many patients will deny difficulties if the question is presented in the latter format. Direct questioning is most effectively achieved by asking the patient about a mid-scale response, for example, "can you read bus numbers or road signs?" A second response can then be offered depending on the patient's answer. For example, if they *can* read bus numbers and road signs, the patient would next be asked "can you read small print or text on the television?" The clinician can then move up or down the response scale until the most appropriate answer becomes apparent. It is also important for the precise sense of each question to be conveyed in different languages to allow feasible comparison between international centres and inter-rater variability to be kept to a minimum.

Specific points

1. Vision

This question asks about vision with full correction (with either glasses or contact lenses). It considers any visual disability irrespective of the underlying cause (e.g. diplopia, severe ptosis) and is therefore not limited to difficulties resulting from worsened acuity.
2. Hearing

This assessment *does* include asking about the improvement of hearing with a hearing aid. Therefore it important to ask patients about the use of hearing aids at the beginning of the question.

3. Speech
No additional instruction.
4. Swallowing
No additional instruction.
5. Handwriting
If the clinician is unsure about the patient's handwriting ability, the patient can be asked to write a simple phrase (e.g. 'the black cat') and an assessment made accordingly.
6. Cutting food and handling utensils
This question, like all in this section, monitors the patient's level of *disability* rather than their underlying impairment. Therefore a score is assigned according to their functional ability irrespective of the underlying contributing cause (e.g. myopathy, impaired cognition or co-ordination). This concept applies also to dressing and hygiene.

For this particular question it is important to note that any effect on meal duration must be due to loss of ability to cut food and handle utensils rather than any other underlying problem such as dysphagia, for example.
7. Dressing
Rate function irrespective of the contributing factors as above.
8. Hygiene
Rate function irrespective of the contributing factors as above.

It is important that the patient is asked specifically about the use of a bath or shower. If patients do not take baths, the examiner should enquire about the reason for this- an avoidance of baths because of their disability indicates a significant degree of functional impairment. It is also important to enquire about bathroom modifications as this information may not be volunteered.
9. Exercise tolerance
The patient should be asked how far they can walk at a reasonable pace before needing to stop to rest. Function is again rated irrespective of the underlying contributing factors (e.g. dyspnoea, myalgia, weakness). It is important to ask the patient to give examples of how far they think they can walk and if necessary, highlight distances within the hospital or the surrounding area to allow this assessment to be made. This question achieved poorer inter-rater reliability than most and therefore requires special attention to obtain an accurate answer.
10. Gait stability
Rate function irrespective of the contributing factors (e.g. ataxia, weakness).

Section II: System Specific Involvement

This section rates function according to the **patient interview** (plus caregiver interview if a patient's cognition is impaired), **clinician's knowledge** of the patient and the **clinical notes**. For example, a patient may volunteer that they had a stroke six months earlier but the exact timing, the nature of the stroke, and the radiological and clinical features are important and must be sought.

Each enquiry should take into account the situation for the **preceding twelve month period** only unless otherwise stated in the question. In some cases a past history of system involvement is also important.

1. Psychiatric

This is largely self-explanatory. However, reactive depression may be managed differently in different countries. In the UK there is an extensive general practitioner's scheme and thus patients would initially be seen and assessed by a general practitioner. Only patients with severe depression or other psychiatric symptoms would subsequently be referred to a psychiatrist for specialist advice. This explains the distinction between categories 2 and 3.

2. Migraine Headaches

This should be assessed on or off treatment, i.e. if the patient is on treatment, they should be asked about the occurrence of migraines on treatment. 'Migraines' are given a broad definition and include those associated with stroke-like episodes and seizures. To facilitate more accurate recall, this question covers the **preceding three month** period and asks how many days migraines have prevented the patient from **functioning normally** at school, work or in the home. If a patient has *not* experienced migraines in this time period, it is important to enquire about any past history of them.

3. Seizures

Again this should be assessed on or off treatment. It is important to ask specifically about absence seizures and myoclonus and whether or not these affect function, as many patients do not volunteer this information. If a patient has *not* experienced seizures over the preceding twelve months, it is important to enquire about any past history of them. Patients often do not know the classification of their seizures and thus assignment of the appropriate score is left to the discretion of the clinician.

4. Stroke-like episodes

Since we are looking specifically at the effects of mitochondrial disease, it is important to exclude focal deficits likely to be due to cerebrovascular disease or cardiac embolus. The classification is based upon history, examination and review of the clinical notes, in particular cerebral imaging.

5. Encephalopathic episodes

This will likely be relevant to only a small proportion of patients. The definition of encephalopathy is as suggested in the responses. This question only covers the previous **twelve months**.

6. Gastrointestinal symptoms

No additional instruction.

7. Diabetes mellitus

It is important to ask specifically about transient or gestational glucose intolerance.

8. Respiratory weakness

This should be assessed using a fixed or hand-held spirometer. We advise asking the patient to repeat the forced vital capacity (FVC) three times and then using the second or third FVC, whichever is higher, as their reading.

It is important to find out the patient's height and age. Using this information, the predicted FVC can be calculated using the following equations:

Male:

Female:

Respiratory scores are then assigned according to the percentage of the predicted FVC the patient attained.

9. Cardiovascular system

In patients with mitochondrial disease, we recommend regular cardiovascular screening to look for cardiac hypertrophy or cardiac conduction defects. This question is based upon ECG or echocardiogram changes and thus requires review of the clinical notes. Clinical and ECG assessments should be within the last 12 months. The last available echocardiogram is acceptable but abnormal studies (or those associated with new changes in clinical or ECG parameters) should be repeated at least every 2 years.

Section III: Current Clinical Assessment

This section rates the patient's **current status** according to the examination performed by the rater. Scores are therefore assigned **according to the clinician's**

judgement and the patient's and carer's subjective opinions are not taken into consideration.

1. Visual acuity

This assessment is performed whilst the patient wears their usual glasses or contact lenses. We recommend the use of a Snellen chart held at 2.4 metres from the patient (therefore adequate for most examination rooms). Attempt should be made to measure this distance as accurately as possible.

The responses consider the Combined Snellen Denominator (CSD) e.g. acuity of 6/12 in one eye plus 6/18 in the other gives a CSD of $12+18 = 30$. For visual acuities equal to or less than 6/60 (e.g. finger counting), 60 is used as the denominator for calculating CSD. This 'ceiling' prevents complete blindness in one eye scoring 5 and preventing documentation of further disease progression in the better eye.

2. Ptosis

This should be examined without the use of mydriatic eye drops. The examiner must enquire about previous surgery correcting the ptosis.

3. Chronic progressive external ophthalmoplegia

No additional instruction.

4. Dysphonia/Dysarthria

This is most often assessed during conversation but may be assessed more formally if this is deemed necessary.

Questions 5 to 9 enquire about myopathy, cerebellar ataxia, neuropathy, pyramidal and extrapyramidal disorder; i.e. impairments which may each cause the patient to become wheelchair bound. The assessment of a particular impairment may become difficult when other impairments are contributing to the patient's disability. In this case a clinical judgement must be made as to how the patient would score if they were not affected by other impairments. For example, a patient who appears wheelchair bound due to severe ataxia may also have a myopathy, but a clinical judgement must be made as to what the patient would score for myopathy if they were not affected by ataxia. In this example, a patient with MRC grade power of 4/5 would not score 5 for myopathy

5. Wheelchair dependent **primarily** due to proximal weakness.

as the myopathy alone would not be expected to cause a loss of ambulation. Similarly, the ataxia may not appear severe enough on its own to cause a loss of ambulation, and hence ataxia may not score 5 either, the assessment concluding that a combination of myopathy and ataxia have caused the patient to be wheelchair bound.

5. Myopathy

The assessment of myopathy has been developed to allow completion within a normal outpatient examination room. It is particularly important to follow

these instructions as this question's scores showed more variability between raters than most. Assessment of shoulder abduction is performed with the patient sitting with their shoulders abducted to 90°, hands into their chest. Hip flexion is assessed by asking the patient, who is seated with their knees flexed at 90°, to lift each leg individually against resistance. Rising from a 90° squat equates to a person standing up from a chair of normal height without assistance and with their arms folded across their chest.

6. Cerebellar ataxia

This should be assessed by standard clinical examination. The safety of a patient during heel-toe walking should be considered.

7. Neuropathy

Particular attention should be paid to the presence of proprioceptive loss and a resultant sensory ataxia. For example, in some patients with autosomal recessive POLG mutations, a sensory neuronopathy (dorsal root ganglionopathy) may be the prime reason for a loss of ambulation (score 5), with the cerebellar ataxia and myopathy that are often present scoring much lower as neither alone would be so disabling.

8. Pyramidal

No additional instructions.

9. Extrapyramidal

This is based upon the well established Hoehn and Yahr staging for Parkinson's disease.

10. Cognition

Specific instructions are given for each of the cognitive tests. The Wechsler Test of Adult Reading (WTAR) is only performed on one occasion since it is a pre-morbid test of intelligence. The Symbol Search (SS) and Speed of Comprehension Test (SOCT) should be performed each time the scale is administered. These cognitive tests are fairly user-friendly for most patients. Patients with significant visual impairment or severe muscle weakness or ataxia affecting their ability to write may find the tests more challenging. In these circumstances the physician may help fill in the answers, but must not prompt the patient. For severely blind patients the SOCT may be read out, but the SS cannot be performed. For severely blind and deaf patients, both tests may not be able to be performed and should be documented as such. Because the NMDAS measures disease progression, the patients individual scores (minus those that were unable to be performed) can still be compared longitudinally.

Section IV: Quality of Life

Quality of Life is considered to be a very important health outcome and thus is of great importance to mitochondrial disease patients. It is assessed using the SF 12v2 - a standard, extensively validated questionnaire which comes complete with its own administration and scoring manual. This questionnaire should be completed by the patient or their carer each time the NMDAS is administered. There should be no input from the clinician or health professional as this survey assesses the patient's own opinion of their health status. If time is limited during the clinic appointment, patients can be asked to complete the questionnaire in the waiting room or can take it home and return it by post.

Scoring

Each question in the NMDAS has a possible score from 0-5. Each of the first 3 section scores are calculated by simply summing the scores obtained for each question in that section. The higher the score the more severe the disease.

The Quality of Life Section undergoes separate scoring as detailed in the SF manual. It is helpful to present the scores for each section rather than simply referring to an overall score for the whole scale. At the very least, it is imperative that the quality of life score obtained on the SF-12v2 is presented separately from the disease score obtained in sections I-III.