New EAN Guidelines: Diagnosing HyperCKaemia, Managing Amyotrophic Lateral Sclerosis, and Addressing Neurogenic Dysfunction

Authors:	Jivitesh Newoor, EMJ, London, UK

Citation:	EMJ Neurol. 2023;11[1]:17-20. DOI/10.33590/emjneurol/10305297. https://doi.org/10.33590/emjneurol/10305297.

DURING the 9th Annual Congress of the European Academy of Neurology (EAN), 1st–4th July 2023, a highly important session entitled 'Meet the New EAN Guidelines' featured the most recent guidelines developed by EAN over the past year. These guidelines, currently in the pipeline, are carefully prepared by ad hoc Task Forces following a well-established procedure.

GUIDELINES ON THE DIAGNOSTIC APPROACH TO OLIGO- OR ASYMPTOMATIC HYPERCKAEMIA

Theodoros Kyriakides, University of Nicosia, Cyprus, discussed the evolution of hyperCKaemia investigation, noting that the 2010 European Federation of Neurological Societies (EFNS) guidelines relied on muscle biopsy as the diagnostic gold standard, despite its invasiveness and susceptibility to sampling errors. Currently, their objective is to gather information in a minimally invasive, highly sensitive, specific, and cost-effective manner. Notably, genetic diagnosis has become more feasible and desirable, owing to advancements in next-generation sequencing (NGS).

Who to Investigate

When evaluating hyperCKaemia, exploring non-neuromuscular and non-myopathic causes is recommended. Clinicians should also inquire about any family history of neuromuscular disease, hyperCKaemia, or malignant hyperthermia. To ensure accurate assessment, it is advised to repeat creatine kinase (CK) measurements after at least 72 hours, preferably after a week of abstaining from exercise, medications, or other factors that could elevate CK levels. Additionally, CK should be repeated twice, with 1-month intervals after the initial measurement.

"When evaluating hyperCKaemia, exploring non-neuromuscular and non-myopathic causes is recommended."

How to Investigate

In the diagnostic approach to hyperCKaemia, several tests are recommended to investigate the underlying causes. For suspected metabolic myopathy, a screening test including dried blood spot, acyl carnitine profiling, and measurement of resting/exercise lactic acid levels is advised. Nerve conduction studies and electromyography are recommended to identify any myopathic basis of hyperCKaemia. Muscle MRI can be used to assess abnormalities, guiding genetic testing based on observed patterns.

Genetic testing is recommended in specific scenarios, such as juvenile/adult onset, CK levels exceeding three times the upper limit of normal, myopathic electromyography findings, abnormal muscle MRI scans, and females with hyperCKaemia. For cases without known family mutations or individuals with characteristic

clinical phenotypes, targeted single gene analysis may be considered for paucisymptomatic or asymptomatic hyperCKaemia. NGS is preferred over sequential targeted DNA testing. In certain cases, a muscle biopsy may be necessary for comprehensive phenotyping and exploring the transcriptome to understand the consequences and mechanisms of variants detected through NGS blood testing.

GUIDELINES ON THE MANAGEMENT OF AMYOTROPHIC LATERAL SCLEROSIS

Philippe Van Damme, Katholieke Universiteit (KU) Leuven, Belgium, highlighted the unmet care needs in amyotrophic lateral sclerosis (ALS) management, owing to the limited availability of pharmaceutical interventions. Van Damme then presented the new ALS guidelines, which replace the previous guidelines on ALS in Europe that date back to 2012.

Recommendations

Concomitant frontotemporal dementia

The presence of concomitant frontotemporal dementia in ALS can impact decision-making. Therefore, it is crucial to assess the individual's capacity to make decisions, as well as provide consent, and evaluate the severity of frontotemporal dementia and cognitive problems. It is also important to consider the individual's acceptance and ability to cope with the treatment.

Multidisciplinary care

The guidelines offer specific recommendations regarding the composition of a multidisciplinary team, primarily based on the National Institutes for Health and Care Excellence (NICE) guidelines. An optimal team should consist of various professionals, including an ALS neurologist, respiratory specialist, nursing professional, mental health professional, social worker, speech/language pathologist, dietitian, and physical therapist.

Disease-modifying treatments

The panel recommends offering lifelong riluzole to all individuals with ALS at the time of diagnosis. Dose adjustments and re-evaluation should be considered in case of adverse events. The use of cell-based treatments outside of clinical trials is not recommended until positive Phase III trial data become available. However, temporary recommendations are made for two promising new drugs, edaravone and AMX0035, while awaiting the final outcome of Phase III

studies. Tofersen is recommended as a first-line treatment for individuals with ALS caused by pathogenic mutations in superoxide dismutase 1, with the acknowledgment of potential severe adverse events.

"The panel recommends offering lifelong riluzole to all individuals with ALS at the time of diagnosis."

Nutritional support

Although there are currently no ongoing randomised controlled trials specifically focusing on nutritional interventions, the guidelines recommend early and regular discussions about the potential option of gastrostomy as the disease progresses. These discussions should consider factors such as swallowing difficulties, weight loss, respiratory function, and feeding-related challenges. The guidelines highlight the benefits of early gastrostomy placement and emphasise the risks associated with delaying the procedure.

Respiratory symptoms

Initiating non-invasive ventilation is recommended for all patients with ALS who exhibit symptoms, signs, or laboratory findings suggestive of respiratory insufficiency. However, diaphragmatic pacing is not advised as a treatment for ALS.

Symptomatic treatments

Sodium blockers, such as ranolazine, quinine sulphate, mexiletine, and carbamazepine, can be considered for managing muscle cramps. Non-pharmacological approaches and physical therapy are recommended for spasticity. Cannabinoids, baclofen, tizanidine, dantrolene, or gabapentin should be considered to treat muscle stiffness, spasticity, or increased tone. Botulinum toxin may be considered for focal spasticity cases.

When treating sialorrhoea, additional symptoms or comorbidities (such as dysphagia, dysarthria, and depression) and potential adverse events should be considered. First-line treatment options include anticholinergics.

Dextromethorphan/quinidine may be particularly suitable for individuals with emotional lability or pseudobulbar affect. In severe cases of sialorrhoea unresponsive to pharmacotherapy or poorly tolerated, botulinum toxin can be considered. Radiotherapy may be an option if other treatments have failed.

Future Updates

The updated EAN guidelines on ALS management are expected to be published by the end of 2023, and will provide a comprehensive framework for ALS management and highlight areas requiring further research. Given the rapidly evolving treatment landscape and the evaluation of three additional drugs by the European Medicines Agency (EMA) in the coming year, Van Damme anticipates the necessity for future updates to the guideline.

MANAGEMENT OF NEUROGENIC LOWER URINARY TRACT AND SEXUAL DYSFUNCTION FOR THE PRACTICING NEUROLOGIST

Jalesh Panicker, University College London Hospitals (UCLH), UK, explained that these guidelines aim to provide evidence-based recommendations for the management of neurogenic urinary and sexual dysfunction specifically tailored for practicing neurologists. Currently, the guidelines previously established by various societies have had limited implementation in general neurological practice.

Assessment of Bladder Symptoms

Neurologists are advised to proactively inquire about bladder symptoms and conduct a targeted physical examination during the initial evaluation of such symptoms. Urinalysis should be conducted at the initial evaluation and as needed during follow-up visits, with urine culture reserved for suspected urinary tract infections. Completing a 3-day bladder diary is recommended. Measurement of post-void residual volume should be performed using non-invasive methods. Renal function tests, including blood urea and serum creatinine levels, are advised. Annual testing is recommended for individuals at risk of upper urinary tract damage. Prostate cancer screening may be offered to males over 50 years old. Urodynamics testing is not recommended initially, but should be considered for individuals at high-risk or those with atypical symptoms. Referral to specialists

is warranted for patients at risk of upper urinary tract damage, suspicion of concurrent primary urological pathology, poor treatment response, or significant side effects from first-line bladder symptom treatments.

Treatment of Bladder Symptoms

Neurologists should provide guidance on fluid intake and offer bladder retraining for individuals with urinary urgency and spontaneous voiding. Advice on pelvic floor exercises should be suggested to those experiencing urinary urgency and/or stress incontinence. Appliances can be offered to improve continence in select individuals. For individuals who do not respond well or cannot tolerate other treatments, tibial nerve stimulation may be offered, whilst taking patient preference into consideration. The benefits and potential risks and burdens of these interventions should be discussed.

Intermittent catheterisation should be offered as the first-line therapy to individuals unable to empty their bladder. In cases where long-term indwelling urinary bladder drainage is unavoidable, suprapubic catheter drainage is preferred over urethral catheterisation. Routine antibiotic prophylaxis is not recommended for catheter users. Symptomatic urinary tract infections in catheter users should be treated with antibiotics, guided by urine culture/sensitivity. Antibiotics are not routinely recommended to treat asymptomatic bacteriuria, except in specific circumstances. Antimuscarinic drugs should be offered to individuals experiencing urinary storage (overactive bladder) symptoms, and β3 receptor agonists may also be considered for such symptoms. However, there is insufficient evidence to recommend the use of cholinergic drugs to promote bladder emptying in individuals with detrusor underactivity. Desmopressin may be offered to those experiencing nocturia or nocturnal polyuria that significantly affects their quality of life.

Assessment of Sexual Symptoms

Neurologists should actively inquire about sexual problems and conduct targeted physical examinations during regular assessments. Screening laboratory tests, such as for vascular risk factors in males with erectile dysfunction, should be performed when clinically appropriate. Routine measurement of testosterone is not recommended unless hypogonadism is suspected. Instrumental diagnostic evaluations, such as pelvic neurophysiology and MRI, are not routinely needed for initial workup but may be considered in specific cases. Referral to specialists is advised for patients with specific concerns or conditions that impact sexual function.

Next Steps

Panicker emphasised the importance of neurologists managing symptoms and recognising when specialist referral is needed. While the guidelines do not encompass intricate assessments, they provide guidance on history-taking, basic bedside assessments, and the use of first-line oral agents, which are within the scope of practice for neurologists. The next steps involve the steering committee reviewing outcomes, making necessary modifications, and developing management algorithms, which will then be submitted for publication by the Guideline Production Group.

CONCLUSION

The newly introduced EAN guidelines, developed with rigorous methodologies, emphasise the importance of accurate assessments, personalised approaches, and the involvement of specialised teams to enhance decision-making and improve patient care. The guidelines also highlight the need for future updates and further research. ●