MEETING REPORT
July 2024

Thank you

To the organisers and hosts:

Professor Ruth Walker
Professor Dr. Adrian Danek
Dr. Kevin Peikert

To all our speakers!
To everyone who sent in patient related questions, and to the international panel who answered them.

To all attendees and everyone reading this report and helping to share the knowledge.

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INTRODUCTION

The Forum was moderated by Professor Ruth Walker, Department of Neurology, Mount Sinai School of Medicine, New York, USA.

The main presentation titled 'Nutritional Challenges among people with feeding dystonia' was given by the guest speakers:

- Dr Martin Paucar Arce, Department of Clinical Neuroscience, Karolinska Institutet & Department of Neurology, Karolinska University Hospital
- Dr Josefin Kyhle, Speech and language pathologist, Department of Neurology, Karolinska University Hospital, Stockholm, Sweden.

They then joined a specialist panel together with:

- Professor Dr Adrian Danek, Ludwig Maximillian University (LMU), Munich, Germany
- Dr Elina Tripoliti, Clinical Specialist Speech and Language Therapist, University College London (UCL), UK.

The patients, their family members and carers sent questions prior to the meeting which were answered by the panel.

PRESENTATION

Dr Paucar started with a summary of knowledge to date about VPS13A and XK diseases. There are six known patients in Sweden diagnosed with VPS13A (four of them at their center in Stockholm) and two patients diagnosed with XK disease. Various case studies were presented explaining the specific circumstances of each of them.

The feeding dystonia was described from a clinical point of view as:

- involuntary tongue protrusion during eating (for reference see published paper in Movement Disorders, volume 25, issue 1)
- it can be variable and it can recede spontaneously
- it can be unresponsive to drugs.

Feeding dystonia can appear in patients diagnosed with other movement disorders.

From patients' point of view feeding dystonia is described as: unpleasant when eating, whether at home or in public; frightening; fear of chocking; repeated biting.

The repeated biting of the lips, tongue and cheeks can be alleviated by using a mouth guard. There are also some sensory tricks which could be used to alleviate dystonia, such as placing a toothpick, a straw or a small piece of cloth in the mouth.

Feeding dystonia can contribute to weight loss. Therefore, it is important to determine and adapt the type of diet suitable for each individual, depending on the degree of dystonia manifested. This will prevent the malnutrition and weight loss and should improve the overall quality of patient's life.

Some patients responded to botulinum toxin injections at the base of the tongue; however, these are to be administered under careful consideration and there is no scientific evidence that it would help every patient. It is possible that it will induce dysphagia (see below for definition and details) or worsen it, if already present.

Dr Paucar shared a list of medications which were trialled on their patients, but there were no successful results in alleviating dystonia. These were: neuroleptics (Haloperidol and Risperidon), benzodiazepines (Diazepam and Clonazepam), tetrabenazine, levetiracetam, tetrahydroxyphenidyl, dantrolene, cannabis (at patient's express request).

Dr Josefin Kyhle then went to explain dysphagia, the difficulties of swallowing caused by involuntary movements of the muscles in the tongue, mouth and/or throat, which may appear in people with NA syndromes.

Dysphagia is commonly associated with symptoms such as: delayed swallowing reflex; difficulty chewing; coughing while eating/drinking; sensation of food being stuck in the throat/chest. These may lead to weight loss, recurrent pneumonia, and changes in eating patterns.

To prevent / treat these effects it is recommended to consider:

- modifying food texture to help swallowing (see Fig. 1 for details)
- using thickened liquids; these can also suitable for taking oral medication with (crush the tablets where possible, preferably check with a doctor/pharmacist first)
- adapting meal sizes, eating smaller portions more frequently
- fortifying meals with fats, extra sauce and/or condiments
- opting for drinks with caloric content (juice, milk, soda)
- optimising posture while eating/drinking to help move the food from the mouth to the stomach
- using feeding aids: utensils with special grip, drinking cups, safe straws, high-side plates, etc.
- administering oral nutritional supplements
- monitoring the levels of nutrition and hydration, especially when modifying food and/or drink textures.

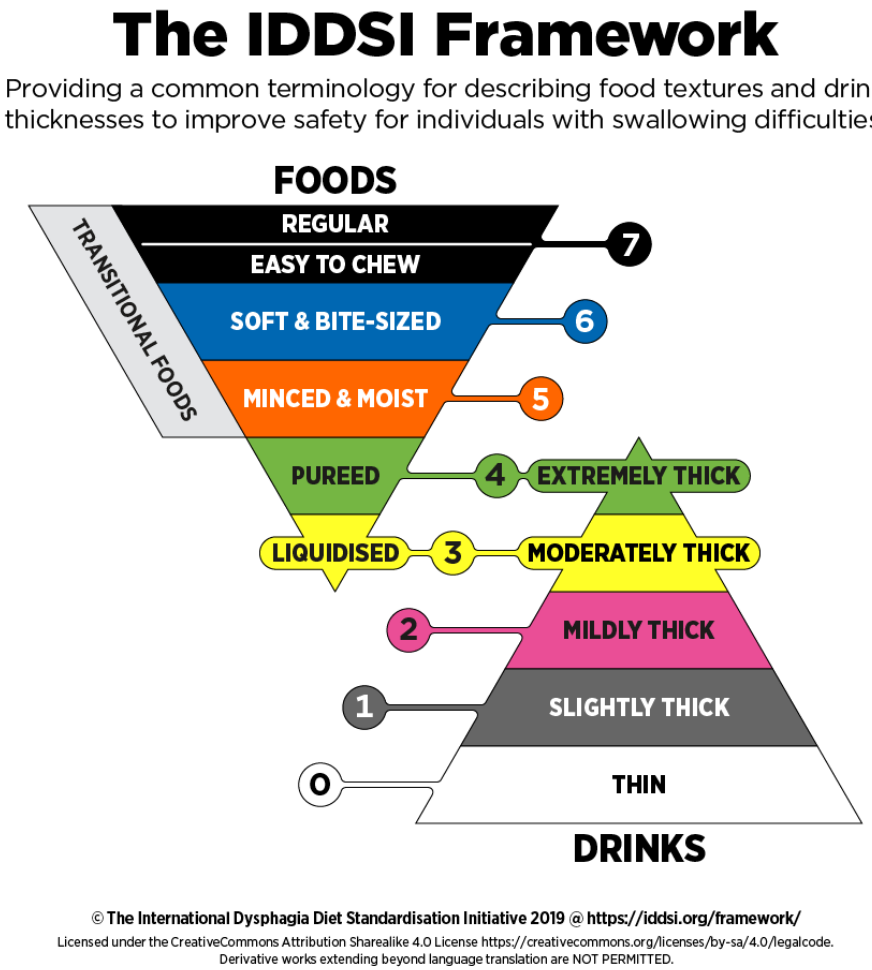

Fig. 1 – Food texture definitions

For the patients able to eat/drink only very small amounts or not at all orally, it is extremely important to ensure a good oral care comprising of:

- brushing and flossing teeth
- using saliva substitutes (pills, moisturising gels, spray)
- using mouth/oral swabs to lubricate the mouth.

These measures will reduce the risk of pneumonia through the aspiration of oral bacteria.

Dr Kyhle also mentioned that Percutaneous Endoscopic Gastronomy (PEG) may also be an option to ensure the delivery of optimal nutrition to the patient. This is a procedure through which a feeding tube is placed to provide the optimal nutrition to the patient. These are called PEG tubes or G tubes. Read detailed information about this procedure in our previously published Report of the 15th VPS13 Forum (pages 3 – 4).

Dr Paucar concluded that it is unknown how common feeding dystonia can manifest in people diagnosed with either of the NA syndromes, even with the support of AI tools. There is also no other conclusive data about association with specific gender of the patient, other specific symptoms or any other mechanisms associated with the NA conditions.

Based on the data collected from the six genetically diagnosed patients (four with VPS13A disease and two with XK disease) at the Karolinska University Hospital, half of them (three cases) had previously manifested feeding dystonia, which then receded spontaneously. This is how the idea of creating a rating scale for feeding dystonia (to take into consideration symptoms and factors discussed here above) appeared and it's currently discussed between professionals at the Karolinska Institutet. Any suggestions and ideas are welcome from those interested.

Q&A SESSION

Patients, family members and carers submitted questions prior to the meeting on a mix of topics, ranging from affecting newly diagnosed patients to patients diagnosed a number of years ago. Some of the questions were already answered through the presentation given by Dr Paucar and Dr Kyhle.

For ease of reference, we will use these abbreviations:

Professor Ruth Walker – RW
Professor Adrian Danek – AD
Dr. Martin Paucar – MP
Dr. Josefin Kyhle – JK
Dr. Elina Tripoliti – ET

RW explained that feeding dystonia may be a term not so widely used in descriptions of symptoms of patients diagnosed with either of the NA syndromes. So it may be that searches in the published research literature may not always return accurate results, and further investigation may be needed. She also clarified that the speech and swallowing difficulties of patients with dysphagia may be not only due to tongue muscles, but also due to the discoordination of other muscle groups located further back in the digestive system. She then invited JK and ET to speak about exercises for the muscles of speech and swallowing.

Question 1 – What can patients do proactively to try and improve these types of dysphagia symptoms?

Answers:
JK – She has experience only with patients at a later stage after diagnosis. Muscular and articulatory training for the mouth and the voice started as early on as possible are likely to have a positive impact on the speech and swallowing functions in the longer term. If these functions are already significantly affected, some compensatory strategies should be considered to ensure that the patients can make themselves understood and can communicate their needs, so a high degree of presonalisation of the therapies may be required. Augmentative and alternative communication (AAC) devices can be helpful, i.e. text to speech conversion devices or computer assisted speech technology.

ET – She has experience working with Alex Irvine, the daughter of the founders of the charity, and also other cases which came through the NHS (UK National Health Service) system. Each individual is different and has specific needs to be met. She agreed with MP that there are instances when the dysphagia and swallowing problems resolve spontaneously.

From experience, positive results can be achieved by educating the patients, their families and carers about the swallowing mechanism and concentrating on the pre-swallow, the preparation of the whole meal experience. Explaining how the tongue works and practical demonstrations where possible will empower the patient to gain perspective and bring more control over the actual mechanism of swallowing.
In the initial stages, the majority of the issues are of an oral nature, not esophageal. It's recommended to explore which senses are more likely to create tongue protrusion. It could be the texture, the temperature or the taste of the food and/or drink. It's also important to take into consideration the level of anxiety the tongue protrusion can create in anticipation of the meal. So it's important to start creating a relaxing environment before the meal.
When applying this approach to her patients, the majority of them seemed to have resolved the swallowing issues somewhat spontaneously, after about 3-4 months of education and therapy.
Another recommendation to solve swallowing issues is to use the expiratory muscle strength training (EMST) device. This is similar to blowing a balloon, but there is a mechanism to control pressure. While there is no research data about its specific use in people diagnosed with NA syndromes, there is some data about usage in people diagnosed with Parkinson's disease. From practical experience, the EMST device exercises the upper respiratory muscles (used in coughing) which improves the coordination of breathing and indirectly, it gives a good lip-seal exercise. She also found it to be useful for saliva control and clearing of the throat.

RW – In conclusion, the symptoms of each patient will evolve differently over time. It may be the evolution of the condition itself or it may be the result of other therapies used in treating certain specific symptoms. What benefited one patient may not necessarily benefit another one, even if the circumstances may seem similar.

AD – There is still work to be done regarding the actual definitions. The suggested rating scale is interesting, but there needs to be consistency in the terms used for this. So far there are: tongue protrusion, biting issues and swallowing issues. In addition, there are formation issues, too. There needs to be clarity on how all these mix together, because these phenomena don't necessarily occur altogether.
He referred to some unpublished work of his and Benedikt Bader who looked at 50 – 60 patients with genetic diagnosis of VPS13A disease. The data was collected through questionnaires filled in by patients' treating physicians and based on these, the incidence of dysphagia was around 50-60%.
The aspect of receding dysphagia is a highly interesting phenomenon which is not uncommon, however we don't know the exact neuroanatomical site where this happens. It is likely that it's somewhere in the basal ganglia, but there is no scientific confirmation of this at present.
It would make sense to collect a number of cases to study by applying the latest imaging techniques or Voxel-based morphometry (VBM). [VBM is an automated technique that transforms a brain scan from an individual to a standardised template, to find volumetric differences in small areas (voxels).]
In addition, there are other conditions with similar phenomena. He referred to a series of research work published by Susanne Schneider who looked into different types of neurodegenerations in patients with iron accumulation in the brain. Further conversations are to be had about this offline.

Question 2 – What medication or therapies could help improve chewing and drinking? Is there anything you can recommend about tongue protrusion while eating. The patient is considering Botox on the tongue and medication – any experience with clonazepam.

Answers:
Please refer to pages 3 and 4 in this document and to the details in ET's answer to Q1 (page 5).
Please do remember to consider each case on an individual basis. As patient, family or carer it is important to discuss each option with your treating physician. You may wish to guide them back to this document, especially if they are unfamiliar with the NA syndromes.

Question 3 – How can speech be improved for VPS13A patients? The patient tends to mumble, slur and talk too quickly.

Answers:
ET – In her experience these are treatable. If it's possible, start early on, but understandably this may not always be the case. The symptoms related to speech can fluctuate and are different for each individual. It could start with dystonia and go to Parkinsonian speech, which is very quiet. It's very important to keep speech therapies flexible, adapt and change them depending on the evolution of each patient.
In her experience, ET found that with advanced Parkinsonian symptomatology it helps to treat loudness with Lee Silverman Voice Treatment (LSVT LOUD) LSVT. The concept of Loudness as a useful intensive voice workout from this very well researched program. You can find more information on www.lsvtglobal.com.

AD – Regarding the LSVT this is so far the only evidence-based treatment which should be made available for patients with the symptoms described in the question. It may not necessarily be helpful to the dystonic patients though.

JK – Regarding the sessions with patients, she asked ET how often she sees her patients. ET replied that it depends on the type of therapy program, for instance LSVT has 16 sessions. The patients shouldn't actually be discharged, the therapy needs to continue for as long as required. For some people it can be all too intensive, so she needs to adapt to their rhythm and needs.

Question 4 – What can be done to prevent vocal tics or diminish them? Is there any anything that can prevent the occasional lip smacking or the spitting?

Answers:
RW – Tics are a type of hyperkinetic abnormal involuntary movement where someone has an urge to make a movement. They can be voluntarily suppressed, but they are likely to often come out in a flurry, a burst after they've been suppressed. It's not always clear in each case if the vocal ticks are true ticks, insuppressible by definition, with the urge to make them or whether they're another kind of involuntary movement.
Also, please refer back to details in ET's answer (to Q1) starting on page 5.

Question 5 – Is there anything specific that can be done to prevent the progression of the symptoms mentioned above?

Answers:
RW – There isn't anything specific, however maintaining overall general health is very important. This includes paying attention to the nutritional status, to the physical and mental health, receiving any physical therapy as needed.

MP – The complexity of symptoms clearly varies from individual to individual, and combined with the fact that the NA syndromes are rare, it's not possible to provide 'general recommendations. A course of treatment is usually a collaboration between the treating physician and a number of therapists who can provide support with specific symptoms and subsequently monitor their evolution in time. There are still a lot of questions we don't have the answers for, hence more research needs to be done in this area.

AS – The quality of life and the survival rates are clearly dependent on the quality of care received, particularly the affectionate caring of those around the patient, from their doctors and therapists to their families and carers. The general outlook for patients in such positions is considerably better.

Question 6 – What are your thoughts on acupuncture for VPS13A?

Answers:
RW – In principle, acupuncture is safe to try, especially if you have an experienced practitioner. There are no downsides to trying it, apart from the potential costs. It's challenging enough in rare diseases to try and build up evidence for the conventional therapies, hence there is even less data available on the alternative medicine therapies.

Question 7 – There is wide variation in the degree of symptoms among patients with XK disease. Is it similarly so with VPS13A?

Answers:
RW – As MP highlighted in his presentation, there is a wide variability of symptoms in VPS13A. We also know that there has been published research about several families where siblings are either carrying, or are affected by one of the NA syndromes. However there doesn't appear to be a clear relationship between the genetic mutation and the clinical presentation.
This is a topic of interest to scientists, and they are keen to understand if there is a genotype – phenotype correlation between the mutation and the gene. This could potentially give us insight into the function of the protein. However, there seem to other factors weighing in in both diseases.
In terms of predicting who is going to be affected and in what way, there is currently no way of making such estimations. From the cases known to her and her colleagues, in the families / siblings we know of, there is no pattern that could predict the course of the disease and what the manifestations could be.

Question 8 – And thinking of future generations likely to inherit one these two diseases, is there any way to predict the severity of symptoms?

Answers:
RW – There is more variability with XK than with VPS13A disease. We know of people who have been minimally affected after decades of being diagnosed with XK disease. There are no official stats of scientific evidence, the data we have is based on anecdotal evidence.

Question 9 – Other than maintaining good health, is there any way to minimize later symptoms?

Answers:
The details of the combined answers for Q5 (page 8) cover this question, too.

Question 10 – Is there a chance that, while a person may have the genotype for XK, he / she won't have the phenotype? Are there stats on that?

Answers:
This is covered in context details provided in the answer for Q7 (page 8).

ADVOCACY UPDATES

Despina Dinca, Charity Manager for NA Advocacy gave a brief overview of what NA Advocacy and NA Advocacy USA stand for and what they've been up to in the past few months since the Forum in April.

In July 2024 a new grant was awarded to Icahn School, of Medicine, Mount Sinai, New York, USA. The research project will last two years, until 2026 and it'll focus on research into brain tissue from XK patients. You can read more about this project and its predecessor in NA News issue 45, where you can also discover other articles from the research world as well as featured patient perspectives.

The advocacies are also supporting the development and progress of young scientists interested in NA related fields through the Glenn Irvine Prize in amount of £5,000.

Follow us on social media to stay in touch or let us come into your inbox four times a year through our newsletter.

The advocacies are grateful for the interesting presentations and thanked the international panel for their contribution in sharing and deepening the knowledge with the scientific community and most importantly with the patients, families and carers.

Thank you for continuing to search for clues to a cure, we're honoured to be on this path together!

NEXT VPS13 FORUM

19th Forum - Monday, 28 October 2024, 13:00 – 15:00 GMT (find your local time)
The topic will be focused on VPS13C.
The exact timings and agenda will be confirmed through the zoom invitation from Dr Kevin Peikert.

Thank you!

ADVOCACY FOR NEUROACANTHOCYTOSIS PATIENTS

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