15th VPS13 Forum: Homburg Conference Summary & Q/A

Summary and follow-up discussion of the 11th International Meeting in Neuroacanthocytosis Syndromes for patients, families, and caregivers as well as for researchers who could not attend the meeting.

Ruth H. Walker, Adrian Danek, Lars Kaestner

Medical Q&A for patients/families/caregivers

Open discussion

MEETING REPORT November 2023

Thank you

To the organisers and host:

Professor Ruth Walker
Professor Adrian Danek
Dr. Kevin Peikert

To all our speakers and especially to the clinicians who answered the patient-related questions.

To all attendees and everyone reading this report and helping spreading the word about our work!

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INTRODUCTION

VPS13 Forum is keeping the conversation going just as intended from the very first edition in 2021! The 15th Forum on 20 November 2023 looked at the summary of the 11th International Symposium in September, in Homburg, Germany. It also had a new Q&A session where patient-related questions have been answered by clinicians present. The Forum was chaired by Professor Ruth Walker, Mount Sinai Medical Center, who is also a Trustee of NA Advocacy USA.

SUMMARY OF THE 11TH SYMPOSIUM

The scientific summary of the Symposium was introduced by Professor Lars Kaestner, the host of this edition held at the University of Saarland, Homburg. This has been published in the Tremor Journal and it's recommended reading for the latest updates on VPS13A and XK diseases, including why they are named this now. Ginger Irvine, Chair of NA Advocacy thanked Lars for organising the event.

There is also a non-scientific summary of the Symposium as published on NA Advocacy website and shared widely on both advocacies' social media channels. Few more subsequent articles about it can also be found in 43rd issue of NA News, our newsletter.

Q&A SESSION

Family members of patients from Australia, USA and China submitted questions prior to the meeting. As they were also able to attend the Forum, there were further subsequent questions which were answered by the clinicians present. For ease of reference, we will use these abbreviations:

Professor Ruth Walker	– RW
Professor Adrian Danek	– AD
Professor Hans Jung	– HJ
Dr Julie Kerner	– JK
Questioner	– Q

Question 1 – dysphagia and sleep issues (VPS13A)
Patient (male) diagnosed with VPS13A – how can swallowing difficulties (dysphagia) be treated and improved. The patient receives botulinum toxin injections (Botox) in his tongue every three months. The food comes back up and sometimes out his nose. Also, he manifests loud talking / screaming in his sleep. (The person who asked the original question was in the Forum, so occasionally further clarifications or questions were added in the conversation).

Answers:
RW – It is recommended to observe how the symptoms look after each injection. If there is improvement, then it's a sign that the dosage and frequency are right. If the symptoms become worse soon after the injection, it is recommended to review and adjust those parameters (where the injection is made, the dosage and the frequency).

Q – There is amelioration after the injections. Also asked if there is any other form (tablets) to administer the botulinum toxin.

RW – There isn't another form, and the injections are the best option (although not always comfortable) because of their targeted nature, they are more effective. About the issue of the food coming back up through the nose, this may be an indication that the dysphagia is caused somewhere further in the digestive system.

AD – This symptom may also be a sign of weakness in the palate, and it may be worth investigating further with the help of a specialist clinician. Perhaps a fiberoptic endoscopy may reveal more of the causes.

RW – the symptoms connected to the sleep issues may indicate a connection with an REM sleeping disorder and it may be possible to treat it with a drug in the valium group. This isn't a symptom previously documented in VPS13A.

Question 2 – weight loss (XK)
Patient (male) diagnosed with XK – recently lost weight and muscle mass, and the appetite can vary from meal to meal. Is this normal in XK and would it be a reason to start considering palliative care?

Answers:
RW – There is no clear indication why weight loss appears, but it is quite common. It doesn't appear to be linked to burning more calories due to increased movements. Percutaneous Endoscopic Gastronomy (PEG) is a procedure to place a feeding tube. These are called PEG tubes or G tubes and while it is an invasive method, it is efficient in delivering nutrition to the patient. Because of its invasive nature, it needs to be something that's discussed about and considered as early on as possible, when weight loss occurs. It is harder to recover weight and muscle mass, therefore preventing it by providing adequate nutrition through a PEG tube is a preferable approach. If the patient can consume food, high-calorie food is recommended.

HJ – While weight loss can indicate that the condition evolves, it's not necessarily an indication of an irreversible decline. In his professional experience, the patients expressed a sense of relief when they can have the option of nutrition via PEG tube, understanding that this is helping them. Therefore, it is important and advisable to consider and agree on

decisions about this course of action as early on as possible, even before the symptoms manifest.

AD – He knows of a case of a patient who had the PEG tube feeding and recovered fine going back to their normal weight, so the tube was then removed. It's important to remember that weight loss can be very unpredictable in the course of the disease though. Also, the fact that it appears in a patient it's not necessarily an indication that palliative care should be sought solely for this reason.

RW – On palliative care, the specialised teams are experienced and able to advise on what is a good course of action, what factors are important and need to be considered to ensure a good quality of life and how to maximise these for both the patients and those looking after them.

AD – It's important to remember that palliative care is not necessarily a "one-way road". It is specialised medical care for people living with a serious illness. Palliative care is based on the needs of the patient, not on the patient's prognosis. It is appropriate at any age and at any stage in a serious illness, and it can be provided along with curative treatment. It is focused on providing relief from the symptoms and stress of the disease.

Question 3 – deep brain stimulation (DBS)
Are there cases successfully treated through DBS to lead to improvement of the motor symptoms in movement diseases?

Answers:
RW – DBS treats very specific symptoms, which need very careful consideration and evaluation on an individual basis only. It is mainly used in Parkinson's Disease. DBS uses a surgically implanted, battery-operated medical device called an implantable pulse generator (IPG), similar to a heart pacemaker - to deliver electrical stimulation to specific areas in the brain that control movement, which blocks the abnormal nerve signals that cause symptoms (https://www.ninds.nih.gov/health-information/disorders/deep-brain-stimulation-movement-disorders).

While it may be of some use to patients with a lot of involuntary movements, it will not have a positive effect if patients also have symptoms such as seizures, memory loss or cognitive impairment. It may also worsen walking abilities where present.

The process to determine the exact targeted areas in the brain for the implant is very complex (see the link provided above for details) and it requires very experienced neurosurgeons. And even when those targets are determined, it needs to be considered that the effects of DBS wear off over time and most importantly, the brain structures will change over time.

Overall, extremely careful consideration should be given to using DBS and it will only work in a limited number of cases and circumstances.

AD – There is a need for more systematic studies (past and present, and the relationships among living things through time) to enable researchers to reach more conclusive details.

Question 4 – CRISPR research
How is research going on slowing down or finding a cure for VPS13A and what would this look like? Is CRISPR research working along side our studies? Could they be effective? Gene splicing – is it a possibility to splice the VPS13 gene out?

Answers:
CRISPR stands for Clustered Regularly Interspaced Short Palindromic Repeats – read more about what it means.

RW – Slicing out the gene is not necessarily a solution. There would likely be the need to replace the defective one with a healthy gene and protein.

AD – Clarification on the question, which reads as 'splice out the VPS13 gene's *defect*'. CRISPR is a very new technology and while it's legal in the USA and UK, it's not yet accepted or regulated in many other countries. The UK's regulator has approved the world's first CRISPR gene editing therapy, which aims to cure sickle cell disease and transfusion-dependent β-thalassemia and this dates from November 2023. So it's not only very new, but it's also used for very specific purpose.

JK – There is likely more work required to understand what the mutations are, if and how they can be repaired / replaced and 'spliced back in'.

RW – It's certainly a hopeful path, especially with the accelerations in the field from the past decade. There are lessons to be learned from the research of other brain diseases which found a therapy / cure.

Q – Anthony Bartlett from Olink Proteomics asked if there are foetal forms whose reactivation could be considered using saRNA therapeutics.

AD – He is not aware of any such foetal forms, but it may be worthwhile looking at/for parallel paths.

RW – By parallel with Huntington's disease, the affected protein does, but we don't know exactly what the critical functions are.

AD – He shared details about the Aspire partnering event attended on 17 November 2023 (see our detailed report on that) as some of the things discussed there were novel approaches on RNA activation, which probably are worth exploring through basic science projects.

Question 5 – teeth grinding (bruxism)
Following on from discussions about the swallowing difficulties, a patient's relative present in the forum asked further details about odaxesmus (biting of tongue and cheek during a seizure), as well as how to improve the sleep of the patient (only 3-4 hours a couple of times a day). The patient is a female in her early 30's who's been diagnosed (by genetic testing) less than a year ago.

Answers:
GI – Was there any consultation with a neurologist?

Q – They haven't established a good link with a specialist in a hospital / clinic yet. Is there any treatment out there for this though?

RW – Sometimes the injection with botulin in the masseter (the muscle that closes the jaw) may be helpful to reduce the spasm, but it may not be enough. Sometimes a mouth guard may be helpful. There is some medication which can help with reducing the involuntary movements such as tetrabenazine, valbenazine, deutetrabenazine – the newer variants appear to be better tolerated. This medication has been trialed in HD, but getting the right dosage is very important as they can cause unwanted side effects, so it can only be recommended by a neurologist.

Q – No medication has been tried so far.

AD – A second opinion on the genetic testing result (mutations in VPS13A) is always recommended. For the sleeping troubles, he would recommend an overnight EEG (electroencephalogram) which is a painless recording of the brain's electrical activity during sleep. An epilepsy diagnosis centre may be a good place where this can be done.

CONCLUSION

Please consider sharing your story and/or experiences related to VPS13A or XK disease.

Whether you are a patient yourself, a relative of someone affected or a carer for someone diagnosed, there will be others out there who can benefit from your knowledge and experience. By sharing we continue to raise awareness and reach further in communities where we may be able to help.

Consider asking someone in the medical team looking after a diagnosed patient to write up a case report (they will know the format of this). If you have such a report, please contact us (don't send it to us directly) and we'll put you in touch with a relevant researcher / clinician who can help progressing this to be published in prestigious medical journals.

We are always welcoming your contributions in form of articles, thoughts or experiences to share in our newsletter and on our social media. We will not publicise anything without your express permission.

NEXT VPS13 FORUM

16th Edition - Monday, 22 January 2024
The exact timings and agenda will be confirmed through the zoom invitation from Dr Kevin Peikert.

Thank you!

ADVOCACY FOR NEUROACANTHOCYTOSIS PATIENTS

NA ADVOCACY USA
NEUROACANTHOCYTOSIS ADVOCACY USA, INC.

info@naadvocacy.org

www.naadvocacy.org

www.naadvocacyusa.org