Second neurodevelopmental disorders conference: ADNP and more

Universiteit Antwerpen

University of Antwerp, Belgium

Parent community day:
Friday 13th September, 2024

Foreword by Juliette Squadrani (parent)

The ADNP conference conveyed a powerful message of hope. Ongoing research aims to support our children, with clinical trials currently underway, such as Ketamine in the US, and the Davunetide trial set to begin soon. Additionally, other potential treatments are being explored, which may prove to be transformative in the future.

From a functional medicine perspective, there are accessible nutritional approaches that could greatly benefit our children. Working with a functional medicine practitioner ensures that these are tailored to the specific needs of each child, maximising potential benefits.

As parents, we are not powerless. The German Parent community has come together to raise funds for research, providing a support network and valuable information for both parents and medical professionals. Other parent groups should aim to follow their model to further benefit families and professionals working with ADNP syndrome patients.

Click the links below to watch the conference recordings:

Session 1

Session 2

Session 3

***"It's important to have a strong relationship between scientists and patients through good communication, meaningful research, raising awareness of rare diseases and encouraging donations towards research"*, Claudio D'Incal, Antwerp**

***"ADNP syndrome requires an interdisciplinary care solution. A multidisciplinary team is key for the best care of our patients"*, Lusine Harutyunyan, Antwerp**

***"A standardised care pathway can really help us. We should unite with the care pathway of similar syndromes as the pathway is the same"*, Kelly Verbruggen, Antwerp**

Click these boxes to learn more or read relevant papers

Introduction — Kelly Verbruggen (Antwerp, Belgium)

Kelly welcomed all the participants to Antwerp and we enjoyed some coffee and delicious macarons

Syndrome history — Nathalie Van der Aa (Antwerp, Belgium)

Dr Van der Aa gave us a detailed history of the discovery of ADNP syndrome (also known as Helsmoortel-Van der Aa Syndrome, HVDAS) and the evolution in diagnosis of such syndromes.

Helsmoortel 2014 paper

Syndrome identification used to involve:

- Identification of phenotype differences (*physical traits*)
- Leading to confirmed diagnosis through genotyping (*looking at their genes*)

Now, genetic testing is available for many more syndromes

Dr Van der Aa talked us through the diagnosis of the first diagnosed ADNP syndrome patient

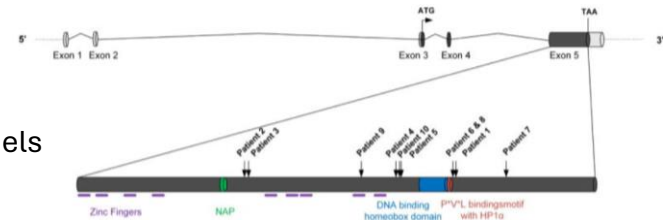
- His DNA was compared to parent DNA which found a 4 base pair mutation in the ADNP gene
- The team went on to study 10 patients with ADNP mutations:

Learn more about genetic mutations

ADNP (activity dependent neuroprotective protein)

- Important component in the brain, involved in the development of the nervous system
- Mice without any copy of ADNP die, and those with 1 copy have developmental issues

The ADNP gene is now included in gene testing panels



Clinical presentation of ADNP syndrome update — Prof. Frank Kooy (Antwerp, Belgium)

Prof. Kooy described recent papers looking into the physical and clinical features of patients with ADNP syndrome

0.17% of patients with ASD (autism spectrum disorder) have ADNP syndrome

Van Dijck 2019 paper

Clinical Presentation of a Complex Neurodevelopmental Disorder Caused by Mutations in ADNP [Van Dijck, 2019]

- This study helped to define common facial features and clinical features, including cardiac abnormalities, behavioural problems, brain MRI abnormalities, feeding and gastrointestinal (GI) problems and visual problems
  - They found large variation in specific clinical features
- Growth parameters were fairly average, but tended towards slightly heavier and shorter
- Over 90% of cases also had ASD

Are certain mutations linked to specific phenotypes?

Dingemans 2023 paper

We don't think so, although the Dingemans team categorised mutations into Type 1 and Type 2, which had possible differences in clinical severity

Molecular perspective — Claudio D'Incal (Antwerp, Belgium)

Claudio gave an overview of DNA, how it makes proteins and the effect of mutations. He took us through patient case studies and introduced davunetide

de novo = a mutation in the DNA code that is not present in the parents

- There are 'hotspots', i.e. *sections of the gene more prone to mutation*, such as tyrosine 719

ADNP mouse models

- Mice missing one copy of ADNP have lower body weight, delayed brain nerve development, and less strong cell skeletons, leading to problems with cognitive abilities

ADNP dysregulates methylation and mitochondrial gene expression in the cerebellum of a Helsmoortel-Van der Aa syndrome autopsy case

D'Incal 2024 paper

- This ADNP syndrome patient passed away following complications from a liver transplantation
- Research suggests there is mitochondrial dysfunction in the ADNP deficient human brain

German crowdfunding money has been used for finding drugs for treating ADNP syndrome in ADNP-cultured blood cells (*cells from humans with ADNP syndrome that are grown in the lab and allow scientists to study the effects of drugs on them*)

Ketamine update

- Low-dose ketamine can increase ADNP protein levels in rat brain cells
- In the human cell model, low-dose ketamine did not increase ADNP protein levels
- High-dose ketamine increased ADNP levels in human cells, but this dose was toxic
- Ketamine appeared to negatively affect nervous cell maturation and the cytoskeleton, even at low doses. This would be detrimental to the ability to learn

Davunetide (NAP, AL-108) update

More on the NAP fragment

Davunetide research

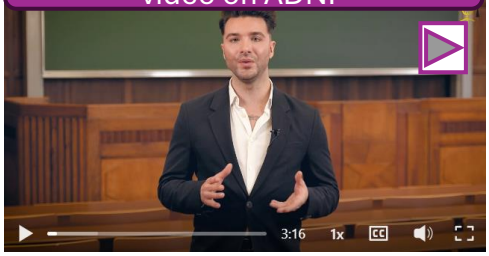
- Davunetide is a neuroprotective fragment of ADNP (ie *can help to restore ADNP activity*) and can be given as an intranasal spray (*in the nose*)
- Mice deficient in ADNP protein were treated with davunetide
  - This reinforced the cytoskeleton (*cell structure)* and improved cognitive function

Next steps:

- Our team are collating blood samples, MRI images, radiologist reports and clinical geneticist reports from all patients, where possible
- **Please send this to our team!**

Action point!

Click here to watch Claudio's video on ADNP



Gait characteristics in ADNP syndrome — Lis Gys (Antwerp, Belgium)

Lis provided a fascinating, detailed description of the analysis of Gait and how motor development issues can affect the normal gait

ADNP physiotherapy overview: study of 13 patients (mean age 11 years [ranged from 8-22])

- Musculoskeletal abnormalities and hypotonia can affect gait (*ability to walk*) and make performing daily tasks more difficult
- Patients with ADNP syndrome often have motor development delay:
  - Walking is delayed in 87%
  - All are now independent walkers but can struggle over long distances
  - Around half struggle to walk on some surfaces and in certain situations

Gait characteristics in ADNP syndrome — Continued...

ADNP physiotherapy overview: study of 13 patients (mean age 11 years [ranged from 8-22])

- Gait analysis found many ADNP children had abnormal gait, due to many factors such as flat footed, low dorsiflex movement, improper knee extension, excess hip/knee flexion
- Some had widened step width (to counteract balance instability) and rotated (outwards) foot position, which can make walking more tiring

Mouse models

- Claudio and Illana stated that they also see gait differences in their mouse models and that there may be a correlation between gait and mutation type (but this is early findings)

Therapy solutions

- Physiotherapy should be tailored to the individual
- Medications (eg davunetide) could improve gait through improved muscle and cytoskeleton

Patient care pathway — Lusine Harutyunyan (Antwerp, Belgium)

Kelly has been developing a best practice 'Patient care pathway' and asked participants to add their thoughts to it (based on the Belgian system). She believes early treatment initiation is very important and can make a big difference Lusine gave an overview of the interdisciplinary care system:

1) Pre-care phase

- Presentation of symptoms, early start of therapy and referrals

2) Diagnostic phase

- Genetics and neurology are involved. Other disciplines join to start treatment planning and provide guidance to patients and their families

3) Treatment phase

- Nutritional support, sleep disorders, support for families (such as financial, carers and schooling)

4) Short-term follow-up

5) Long-term follow-up

- Patients require continuous monitoring, keeping abreast of new medical developments, family support, community support and help with the transition from paediatric to adult care

Functional and lifestyle approaches to autism — Nathalie Van der Aa

Nathalie reviewed holistic medicine (which focuses on physical, mental, spiritual and emotional needs) and the research behind this in autism

Overview

- Complementary treatments need to be individualised to each patient
- There is variable clinical presentation in ADNP patients, therefore different holistic needs
- The mitochondria appears key in a lot of things

Specific modifiable environmental factors in autism

- **Heavy metals**: there is a possible link of aluminium (used as an adjuvant in some vaccines) and mercury to autism
- **Gluten/casein**: some studies have shown behavioural improvements following elimination of gluten and casein from the diet. This may be to do with the gut microbiome (*microbes living in the intestine*). Autistic people have lower microbe diversity and lower amounts of "good" strains of bacteria

Functional and lifestyle approaches to autism — Continued...

ADNP-deficient mouse models

- The microbiome can be impacted by the maternal microbiome during pregnancy, by antibiotic use and nutrition
- This can be improved by reduced C-sections, reduced antibiotic use, better nutrition, improved gut lining and faecal microbiota transplantation (FMT)
    - A parent in the audience shared a success story of FMT in their child

Nutritional deficiencies: autistic people are susceptible to deficiencies

- This can be due to modern diets, restrictive diets, reflux issues, mitochondria problems
- There in an increased need for vitamins, minerals and some macronutrients
- Vitamins B12, B9 and B6 support the increased need for methylation of genes
- One study found B3, B6/9/12, C, D, zinc, iron and magnesium supplementation improved GI symptoms and sleep in autism
- Other supplements include omega-3, carnitine, coenzyme Q10, L-theanine and phosphatidylserine

Nutrition should be personalised to the patient depending on laboratory tests and clinical presentation

Approaches to target the genetic cause of ADNP syndrome — Marc Bühler (Novartis Research Institute)

Marc gave an overview of the Friedrich Miescher Institute (FMI) and a great description into the translation of genetic code into proteins, such as ADNP

ADNP protein is important

- ADNP protein appears important in cell fate decisions (*deciding what sort of specialised cell the stem cells should turn into*)
- Mutated ADNP protein cannot interact properly with other proteins, eg HP1, which affects the ChAHP complex (HP1, CHD4 + ADNP), therefore patients only have 1 functional ChAHP

Therapy options:

1. Promote the production of the correct ADNP protein
2. Remove mutant forms of ADNP
3. Revert (*correct*) the mutation so ADNP can function properly [**best option**]

How can we do this?

- Gene therapy with CRISPR technology, ie edit the mutated DNA directly
    - This is very complex and not well used yet. Some potential to do this in blood cells
- Prevent the ribosome from stopping early (if mutation is causing a premature STOP codon)
    - Aminoglycosides (used as antibiotics) are an option. It works in animal models but there are toxicity problems as the ribosomes can also translate other proteins improperly too
- Edit the mRNA directly
    - ADAR + oligosense nucleotides can be programmed to edit specific portions of mRNA, administered by mRNA vaccine technology
    - Cell models show potential but it has not been investigated in animals yet
    - This would require continuous treatment, not a one-off therapy

Low-dose ketamine in children with ADNP syndrome

Alex Kolevzon (Seaver Center, USA)

Alex joined us via weblink to present the ketamine study data

Ketamine can induce ADNP expression in humans

- Ketamine blocks GABAergic interneurons and increases nerve cell growth factors
- High-dose ketamine can cause toxicity issues, but pre-treatment with low-dose ketamine can protect patients against this

Open-label ketamine study in 10 ADNP children [no placebo group]

Kolevzon 2022 paper

- Low-dose ketamine was used and was relatively safe, adverse events included elation/silly, aggression and fatigue but only lasted 1-2 days
- Well tolerated with no effect on heart rate or blood pressure
- Led to a sustained improvement in ASD symptoms, sensory and ADHD symptoms
  - Note: these were all parent-reported measures so there may be bias
- Ketamine also increases gamma oscillations and 40-Hz auditory steady-state response which are associated with lessened sensory seeking behaviour

Randomised controlled trial is being planned

- The study design has been approved. Patients will be assigned ketamine or placebo, and switch halfway through so all patients receive treatment
- Treatment will be over 4 weeks in the clinic

Davunetide clinical development

Illana Gozes (Tel Aviv University, Israel)

Illana is working with the Exonavis team on davunetide

Davunetide (NAP) is 7% of the ADNP protein – the key active part

- Davunetide interacts with the cytoskeleton and enhances Tau binding by 20-fold
- Mouse models have shown davunetide protects cells from neurodegeneration

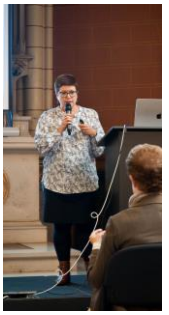
Adult studies with davunetide

- Davunetide has been used in adults with progressive supranuclear palsy (PSP) – this has a similar pathology as ADNP syndrome
- It significantly slows deterioration and provides neuroprotection

Davunetide company update

Vivienne Margolis and Nadya Lisovoder (Galilee-CBR Ltd)

Exonavis are collaborating with Dr Gozes



Animal models: Davunetide has demonstrated safety and efficacy

Human (adult) models: >560 adults have received davunetide, with good safety profile and efficacy, especially in daily living scores and cognitive skills

Upcoming ADNP paediatric davunetide study

- Davunetide is delivered once a day at home over 48 weeks through a nasal spray
- Phase 2/3 study, 66% of patients receive davunetide, 33% receive placebo
- Recruiting in ages 6-16 years and 11 months initially, then extending to ages 3-16 years once initial safety tests are performed
- Recruiting 96 children globally, 10 hospitals are currently signed up

Starting early 2025

Action point!

Tell your paediatrician that you would like your child to be in the study

German Parent Community | Representatives

Christiane and Mauritia told us about the German ADNP parent community

- The group covers German-speaking areas and contains 60 children with ADNP
- A Whatsapp group is used for communications
- They have a patient register, website, hold parent meetings regionally and doctor referrals

Crowdfunding

- The group collected €30,000 through crowdfunding to fund Claudio's research

Group objectives:

1. Networking – with parents, healthcare professionals, therapists
2. Information – for schools, healthcare professionals, etc
3. Donations
4. Contacts
5. Awareness

www.adnp-syndrom.de

Short-term goals: Develop FAQ page on website and an online forum
Long-term goals: Create a network of medical centres and parent associations across Europe

Wrap up | Kelly Verbruggen

The meeting was inspired by the German patient community and Kelly said that Europe should aim to set goals like the German group and copy their great work.

We also need to think how to keep the Antwerp research team funded to keep the research into ADNP syndrome and treatments moving

Report written by Samantha Waite, parent and medical writer by trade. Kind thanks go to Juliette for proof reading, Stephan for the amazing photos, the Scientific Committee, Organising Committee and all the sponsors of the conference