Understanding Chromosome & Gene Disorders

ADNP syndrome (Helsmoortel-Van der Aa syndrome (HVDAS))

rarechromo.org

What is ADNP syndrome and how is it caused?

ADNP syndrome (also known as Helsmoortel-Van der Aa syndrome (HVDAS)) is a genetic condition in which children have autism and developmental delay and/or intellectual disability. ADNP syndrome occurs when one of the two copies of the ADNP gene has lost its expected function. This can be caused by a change ("variant") in the gene or loss of one copy of the gene, or of part of the gene (a "deletion"). This syndrome was first described in 2014.

Genes are instructions which have important roles in our growth and development. They are made of DNA and are incorporated into organised structures called chromosomes. So chromosomes contain our genetic information. Chromosomes are found in cells, the building blocks of our bodies.

The ADNP gene is on chromosome 20 in a band called q13. This gene is important in the development of the brain, and in learning and memory. This is why ADNP syndrome is primarily associated with developmental delay, intellectual disability and autism.

Most children with ADNP syndrome have:

- developmental delay and/or intellectual disability
- autism and sometimes other behavioural difficulties
- delayed or absent speech
- motor delays
- low muscle tone (hypotonia)
- feeding difficulties


Low muscle tone

More information on these and other features is given in this booklet.

Sources and references

The information in this leaflet is drawn from the medical literature including a study of 78 individuals, mainly children, with ADNP syndrome. Key articles used are: Arnett 2018 (https://doi.org/10.1002/aur.1980); van Dijck 2019 (https://doi.org/10.1016/j.biopsych.2018.02.1173); Gozes 2020 (https://doi.org/10.3389/fneur.2020.608444); Siper 2021 (https://doi.org/10.3390/genes12030351). In addition, a number of members of Unique and parents of Dutch children with ADNP have helped in developing this leaflet by filling out a questionnaire about their child. Unique has added comments - in speech boxes - from members of the ADNP Facebook parents group and from Unique. The ADNP parent group has also contributed data from its medical survey.

How many people have this condition?

By June 2022, just over 275 children have been registered in the ADNP Kids Research Foundation Contact Registry. It has been estimated that about 1 per 20,000 of the general population and about 1 per 500 individuals with autism have ADNP syndrome. Whilst most of those diagnosed so far are children, older individuals (up to 45 years old) have been reported. It is thought that, in general, this condition has been under-diagnosed in the past. With the increasing use of the latest 'gene sequencing' technology, it is expected that many more people will be diagnosed with this condition over the next few years.

At the time of writing (2022), the ADNP syndrome Facebook parent group (see back page) had 472 members. This parent group has collected medical data on many children which is reported on the ADNP Kids Research Foundation website.

Appearance

Several features have been reported in individuals with ADNP syndrome. The most frequently observed features are:

- prominent forehead (about two thirds / 70% of individuals)
- thin upper lip (about two thirds / 65%)
- high frontal hairline (about half / 50%)
- broad nasal bridge (about half / 50%)
- short nose (about half / 49%)
- ear malformation (about half / 49%).

"No 'dysmorphic' features." - 9 years old

A number of other features have also been reported and again these vary between children. Children with ADNP syndrome often (70-80%) have early eruption of teeth, with a full set of milk teeth by 1 year of age.

"Dysmorphic' facial features including: eyes – wide spaced and down sloping; ears – posteriorly rotated; relative macrocephaly [large head]; long flat philtrum; thin upper lip; narrow vermilion border to upper lip; flat nasal bridge; hyperteloric; wide spaced inner canthi. Teeth appeared quickly and early, but are small, thin and spaced apart."

Medical concerns

Brain and seizures

In a study of individuals with ADNP syndrome (van Dijck 2019), 59 had undergone brain imaging. Brain anomalies were found in 33 individuals, though the type of anomaly varied. Twelve out of 74 individuals had seizures.

The parent survey showed that 11/39 children have epilepsy. Thirty/40 children have had an MRI brain scan and a brain anomaly was found in 20 children.

> “ The majority of the children in the parent survey who have had repeat MRI scans have shown some form of atrophy and/or white matter loss. ”

Low muscle tone (hypotonia)

Most children with ADNP syndrome have low muscle tone. This can result in a delay in reaching certain developmental milestones such as rolling, sitting, crawling and walking. It may also contribute to the feeding difficulties seen in some children.

> “ My child has hypotonia prominently in his upper body. It affected his lower body as an infant, but improved as a toddler. ”
> - 8 years

> “ He has severe hypermobility in his hands and feet, which are flat with inwards ankles. He needs special shoes and insoles. ”
> - 9 years

Feeding difficulties

Feeding difficulties, such as difficulties sucking, chewing and swallowing are common in children with ADNP syndrome. Some children have gastro-oesophageal reflux in which feeds return readily up the food passage. Constipation has also been reported, as has diarrhoea and frequent vomiting. Some children do not feel full after eating (polyphagia) which involves a risk of obesity (truncal obesity has been found in some children).

> “ My child had problems keeping fluids down as a baby, but no feeding problems now. ” - 8 years

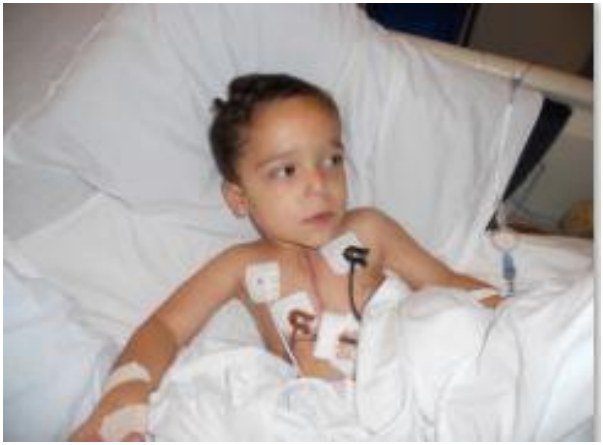
> “ His feeding difficulties come from his sensory issues. ” - 9 years

In 2017, premature tooth eruption was identified as a probable early diagnostic biomarker for ADNP syndrome (Gozes 2017).

> “ The feeding difficulties we see most of in the Facebook group are reflux/GERD (gastro-esophageal disease), oral motor/dysphagia (swallowing and chewing), aspiration, and eating but ‘not feeling full’. ”

Heart conditions

Twenty-six out of 69 individuals (38%) reported in one study (van Dijck 2019) have had heart problems. These varied between individuals. Eleven people were found to have had a hole between the upper chambers (atria) of the heart (atrial septal defect (ASD)). Six people had a joining of the two major blood vessels from the heart (patent ductus arteriosus). Other heart problems were also seen, including floppy heart valves (mitral valve prolapse) and holes between heart chambers (patent foramen ovale, ventricular septal defect).



Recovering from heart surgery

> “ We see a great variety of heart defects in the Facebook group, and our parent survey of 35 children shows heart problems in 60%. My own child has had two corrective open heart surgeries. ”

Eyes and eyesight

Eye conditions are common among children with ADNP syndrome although diagnoses vary. A squint (strabismus) and long sight (hypermetropia) are the most common problems noted. However, not all eye conditions result in impaired vision.

The parent survey in 2016 found that almost 40% of 27 children have suspected or diagnosed cortical vision impairment, this increased to 63% in 2017. Other eye conditions include long sight, near sight, astigmatism, strabismus, and ptosis [drooping eyelid].

Frequent infections

Approximately 50 to 60% (5-6 in 10 children; 19/31 in the parent survey) have had frequent infections, mainly affecting their airways and urinary tract. Some children have frequent ear infections (some are found to have narrow auditory canals).

Development and behaviour

Data from the parent survey showed that:

- 92% of children have a very high pain threshold
- 70% of children have problems regulating their body temperature
- 62% of children have unusually cold feet

In another study:

- 10/11 children have an insatiable appetite (hyperphagia) and need to have their diet monitored
- 7/16 children have an obsession with drinking water and need to be monitored.

Growth

Individuals with ADNP syndrome often have a height within the standard range, but in one study (van Dijck 2019) about one quarter (23%) were reported to have short stature. Some individuals have deficiency of growth hormone or thyroid hormone. Early puberty has been reported in several people with ADNP syndrome.

Sitting, moving and walking

Children with ADNP syndrome usually show a delay in reaching developmental milestones such as sitting and walking. In one study (van Dijck 2019) the average age to sit independently was found to be 13 months, with an overall range of 6 to 60 months. The average age for walking was 30 months, with an overall range of 15 to 72 months.

Sitting and walking may occasionally be more delayed than in the studies published in the medical literature referred to above, according to data from the parent survey.

“ Enjoys walking and playing on the swings. ”

Some children are found to have joint laxity. Others have an altered skull of chest bone (pectus).

4 years

Speech and communication

Almost all children with ADNP syndrome have speech delay. In one study (van Dijck 2019) the average age for first words was reported as 30 months, with a range of 7 to 72 months. One fifth (19%) of individuals in the study did not develop any language skills. In another study (Arnett 2018) of 11 children with ADNP syndrome, children were reported to use gestures and smiles to communicate.

> “ Most children in the Facebook group have mild to severe speech delays. Many severely affected children only have a few words, and a few are non-verbal. My own child started repeating a couple of words around age 3 but could not pronounce them correctly, and had an episode of severe regression at age 4. At 7 he said many words and approximations, but with little function, just copying. ”

Learning

Children with ADNP syndrome show some degree of intellectual disability. The degree can range from mild (roughly 1 in 8 children) to severe (roughly half of children). Toilet training is delayed in most children. Loss of previously acquired skills was reported in one fifth (19%) of people (van Dijck 2019).

The parent survey found that 88% of children have a reported intellectual disability of some degree.

> “ She is functioning cognitively like a 1-year-old. And she forgets things she has learnt previously. ” - 10 years old
>
> “ Many children have had episodes of regression of skills. ”

Behaviour

The majority of children with ADNP syndrome have autism or show autistic traits, although with less severe socialising difficulties than other children with autism. Almost all parents report that during infant and toddler years, children have an extraordinarily happy personality. Repetitive behaviours and restricted interests are commonly observed. Some children have additional behavioural difficulties. ADHD [attention deficit hyperactivity disorder], sensory processing disorder, anxiety, temper tantrums, obsessive compulsive behaviour and mood disorders have been reported. Several children have sleep disruptions that can be severe but which, in some cases, have responded well to treatment with melatonin. Many children with ADNP syndrome have a very high pain threshold. Parents report that the majority (88%) of children with ADNP syndrome are happy and friendly.

“ The parent survey found autism diagnosed in 75% of 28 children. But infants and young toddlers in the Facebook group are described as very loving, affectionate and social with adults, and this loving behavior can cause a delay in diagnosing autism. Some children seem to develop bad behavior characteristics as they grow older that can become severe. Parents describe this as ‘very frustrated, does not listen, does not wait, hits, bites, etc.’. Applied Behavioral Analysis therapy has been successful at reducing these behaviors. My own child was misdiagnosed as having pervasive developmental disorder: because of his loving behavior they felt he did not have autism. However, once a specialized center did ‘gold standard’ testing, he was diagnosed as autistic. ”

“ Very up and down. Controllable if doing what he wants; if not, meltdowns and severe challenging behaviour. Self-harms or others. Also inappropriate friendliness with adults and hates children. Can suffer from anxiety in public. ” - 9 years

“ He is happy, sociable and enjoys playing with children and adults. He is highly sensitive to external stimuli. ”

The parent survey showed that 85% of children have significant sleeping difficulties. Parents believe that this contributes to behavioural difficulties.

What is special about your child?

“ Happy! Loving! Strong! ADNP-Superman! ”

“ Very delayed in her milestones, but when she reaches them, it’s the most special feeling in the world. ”

“ A very cheeky smile! Generally happy if his needs are met. ”

“ Can be so-o-o-o happy. Wants everyone (adults) to smile and laugh with him. But he has almost like a split personality with his severe behaviour, such extremes within seconds - I call him my Jekyll and Hyde. ”

Is there any treatment for ADNP syndrome?

The genetic change causing ADNP syndrome affects development of the brain before birth. Therefore, it may not be possible to achieve a complete cure, even in the future. There is ongoing current research into treatments that may improve some features of the syndrome. At the time of writing, this includes an FDA clinical trial of low dose ketamine which has demonstrated some improvement in several features. There is also animal research suggesting that a peptide-based drug can improve learning and memory deficiencies and muscle weakness (this research was in mice with ADNP syndrome). The best place to learn about the latest developments and obtain information on any clinical trials is the ADNP Kids Research Foundation https://www.adnpfoundation.org/.

Current management recommendations

Having a genetic diagnosis should make it easier to access appropriate monitoring and management. Children with ADNP syndrome should be followed up by a general paediatrician who can oversee care so that development and behaviour can be monitored and the best help given in the form of physiotherapy, occupational therapy, speech therapy, and behavioural therapy. Children should also be followed up by specialist neurological, cardiac or endocrine teams as required.

Why did this happen?

When children are conceived the genetic material (DNA) is copied in the egg and sperm that makes a new child. The biological copying method is not perfect and random changes occur in the genetic code of all children, that are not seen in the DNA of their parents. This happens naturally and is not due to the parents' diet, environment or lifestyle. Most of these DNA changes are harmless. But in rare instances these random DNA changes can lead to health issues or syndromes. When such a random change disrupts the function of the ADNP gene then a child will have ADNP syndrome. Usually ADNP syndrome is due to one of these random (or "de novo") changes. Very rarely, one parent is found to also have the same change (or variant) in their DNA and passed it on to their child. However, it is important to recognize that no one should be blamed for variants in their DNA and no parent is at fault when a new DNA change occurs in their child.

Can it happen again?

The risk of having another child affected by a rare gene disorder depends on the genetic code of the parents. If neither parent is found to carry the change in the ADNP gene, the chance of having another child with ADNP syndrome is very low. However, there is a very small chance that some of the egg cells of the mother or some of the sperm cells of the father carry the change in the ADNP gene. This is called germline mosaicism. This means that parents who are not found to carry the same ADNP change as their child on a blood test still have a very small chance of having another child with ADNP syndrome. This has not been reported in ADNP syndrome in the medical literature so far.

If the genetic analysis of the parents of a child with ADNP syndrome showed that one of them carried the same ADNP change, the chances of it happening again are much higher. Each family situation is different and a clinical geneticist can provide specific advice on the chances of recurrence in each family and, if applicable, options for testing regarding future pregnancies.

Why are there differences in features seen in children with ADNP syndrome?

Although the DNA changes causing ADNP syndrome all affect the function of the ADNP gene, these changes can happen at different places along the gene. Some changes in the ADNP gene have more severe effects on gene function. Also, the ADNP gene is only one of many thousand genes, and there will also be effects from the rest of the genes present in a child. It is differences in our genes that make every one of us unique individuals.

Inform Network Support

Rare Chromosome Disorder Support Group

The Stables, Station Road West, Oxted, Surrey RH8 9EE, UK
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info@rarechromo.org | www.rarechromo.org

Join Unique for family links, information and support.
Unique is a charity without government funding, existing entirely on donations and grants. If you can, please make a donation via our website: www.rarechromo.org/donate Please help us to help you!

ADNP Nonprofit Organization

The ADNP Kids Research Foundation
Incorporated in Washington
EIN# 30-0964243
https://www.adnpfoundation.org/
email: admin@adnpfoundation.org

https://www.adnpfoundation.org/adnp-patient-registry.html

Facebook

ADNP parents group: https://www.facebook.com/groups/ADNPkids

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Unique lists external message boards and websites in order to be helpful to families looking for information and support. This does not imply that we endorse their content or have any responsibility for it.

This information guide is not a substitute for personal medical advice. Families should consult a medically qualified clinician in all matters relating to genetic diagnosis, management and health. Information on genetic changes is a very fast-moving field and while the information in this guide is believed to be the best available at the time of publication, some facts may later change. Unique does its best to keep abreast of changing information and to review its published guides as needed. The text was written by Dr Laura van Dussen, MD, Erfocentrum, Netherlands, and reviewed by Dr Sahar Mansour, Consultant in Clinical Genetics, St George's University Hospital, London UK, and the guide was compiled by Unique.
This guide was updated in 2022 by Dr Maria Jackson, University of Glasgow, UK and Sandra Sermone, ADNP Kids Research Foundation.

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