ADNP related syndrome

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.

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What is ADNP related syndrome and how is it caused?
ADNP related syndrome is a condition in which children have autism and developmental delay and/or intellectual disability. ADNP related syndrome occurs when one of the two copies of the ADNP gene has lost its normal function. This can be caused by a spelling mistake in the gene or loss of one copy of the gene, or of part of it. 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, on chromosome 20, in the band called q12, is important in the development and maturation of the brain. This is why ADNP related syndrome is primarily associated with autism and developmental delay/ intellectual disability.

Most children with ADNP related syndrome have
- autism and sometimes other behavioural problems
- developmental delay and/or intellectual disability
- low muscle tone (hypotonia)
- feeding difficulties

Can this be cured?
There is no cure as the effects of the genetic change took place during your baby’s formation and development. However, knowing this diagnosis means that appropriate monitoring and treatment can be put in place for your child.

Management recommendations
Children with ADNP related 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 is copied in the egg and sperm that makes a new child. The biological copying method is not perfect and occasionally random rare changes occur in the genetic code of children that are not seen in the DNA of their parents. This happens naturally and is not due to your lifestyle or anything you did to cause a change in the ADNP gene. None of the parents of children with ADNP related syndrome who have been investigated have been found to carry the change in the ADNP gene present in their child. The change in the ADNP gene occurred out of the blue (de novo) in their child. A spontaneous change in the ADNP gene cannot be prevented. No environmental, dietary or lifestyle factors are known to cause a spontaneous change in the ADNP gene. No one is to blame when they occur and nobody is at fault.

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. Nonetheless, there is a very small chance that some of the egg cells of the mother or some of the sperm cells of the father carries 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 related syndrome. This has not been reported in ADNP related syndrome in the medical literature so far. If the genetic analysis of the parents of a child with ADNP related 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 give you specific advice on the chances of recurrence in your family and, if applicable, options for testing regarding future pregnancies.

Sources and references
The information in this leaflet is drawn from what is known about approximately 14 children with ADNP related syndrome from the medical literature. Articles used are: O’Roak 2012a; O’Roak 2012b; Helsmoortel 2014; Vandeweyer 2014; Pescosolino 2015. The first-named author and publication date are given to allow you to look for the abstracts or original articles on the internet in PubMed (www.ncbi.nlm.nih.gov/pubmed). 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.

Low muscle tone
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.”

How many people have this condition?
Up to now, approximately 14 children with a mistake in the ADNP gene have been reported in the medical literature. 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.

Aperture

At the time of writing, the ADNP related Facebook parent group - see back page - had 76 members. Parent survey The ADNP related Facebook parent group has collected medical data on approximately 40 children and has reported these medical data on ADNPkids website.

Several features have been reported in children with ADNP related syndrome. Some children have a prominent forehead with a high frontal hairline, a broad nasal bridge and a thin upper lip. Some children may have abnormalities of the hands and feet such as extra fingers or toes, short hands and toes or abnormally curved fingers and/or toes, but this has never been seen in the parents’ group. The type of abnormalities seen vary between children.

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

“No ‘dysmorphic’ features.” - 9 years old
Medical concerns

- **Head and brain**
  Two of the reported children with ADNP related syndrome have epilepsy. Eleven children have undergone brain imaging by MRI. In five of them, the MRI showed abnormalities. However, the type of abnormalities differed between the 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 related 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 old

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

- **Feeding difficulties**
  Feeding difficulties, such as difficulties swallowing and sucking, are common in children with ADNP related syndrome. Some children have gastro-oesophageal reflux in which feeds return readily up the food passage. Constipation has also been reported.

  "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

"The parent survey showed that 11/39 children have epilepsy. Thirty/40 children have had an MRI brain scan. In 20 of them, the MRI scan showed abnormalities.

Behaviour

All children with ADNP related syndrome reported in the medical literature so far have autism or show autistic traits. Some children have additional behavioural problems. ADHD [attention deficit hyperactivity disorder], anxiety, temper tantrums, obsessive compulsive behaviour and mood disorders have been reported. Several children have sleeping problems that can be severe but which, in some cases, have responded well to treatment with melatonin.

"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

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

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The parent survey showed that 85% of children have significant sleeping problems. Parents believe that this contributes to many of the behaviour problems.
**Speech**

Almost all children with ADNP related syndrome have speech delay. Children are often late to start talking and in some vocabulary may be limited. One boy had no speech at the age of 8½ years.

“Most children in the Facebook group have mild – 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 related syndrome show some degree of intellectual disability. The degree can range from mild to severe.

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**Heart problems**

Three out of 11 reported children with ADNP related syndrome have had heart problems. Two had a hole between the upper chambers (atria) of the heart (atrial septal defects (ASD)). Two children had mitral valve regurgitation (leakage of blood from the left lower chamber of the heart through to the left upper chamber). In one of the children this was due to abnormal bending of the valve (prolapse).

“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’.”

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

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“Many children have had episodes of regression of skills.”

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*Recovering from heart surgery*
Eyes and eyesight
Eye problems are common among children with ADNP related syndrome. A squint (strabismus) and long sight (hypermetropia) are the most common problems noted. However, not all eye problems result in impaired vision.

Frequent infections
Approximately 50 to 60% (5-6 in 10 children; 19/31 in the parent survey) have had frequent infections, mainly affecting the airways and urinary tract.

The parent survey found that almost 40% of 27 children have suspected or diagnosed cortical vision impairment. Other sight problems are long sight, near sight, astigmatism, strabismus, and ptosis [drooping eyelid].

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 a new study,
- 10/11 children have hyperphagia [insatiable appetite] and must have their diet monitored
- 7/16 children have an obsession with drinking water and must be monitored.

Development and behaviour

Growth
Children are often of normal height, but some have growth delay and/or short stature. One boy with ADNP related syndrome had growth hormone deficiency [IGF-1 deficiency]. He has been being treated with growth hormone/ somatotropin for two years.

Sitting, moving and walking
Children with ADNP related syndrome usually show delay in reaching developmental milestones such as sitting and walking. Eleven children reported in one study were able to sit independently between 7.5 and 12 months of age and walked between 19 months and 4½ years of age.

Sitting and walking can be more delayed than in the studies published in the medical literature referred to above, according to data from the parent survey. It found gross motor delays in all children. Some children could not sit on their own until 1½ - 2 years. A hundred per cent of children had delays in walking and 15% of those children aged 2-8 are currently still unable to walk. The average age of walking independently was 35 months.

“Enjoys walking and playing on the swings.”