Koolen-de Vries Syndrome Study Weekend
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In late 2015, Unique member Mandy Hazelgrave approached us about the possibility of running a study weekend for families with children and adults who, like her daughter Leanne, have Koolen-de Vries Syndrome (KDVNS). We were keen to help and said that we would try to raise some of the funds needed but the families themselves would also have to fundraise if the weekend were to go ahead. Over the following months, they showed amazing commitment, raising almost £2,000 and we at Unique were pleased to be able to secure a grant of £5,800 from Awards for All, part of the Big Lottery Fund.

Over the weekend of 29th September – 2nd October, 28 families, plus Beverly and Craig from Unique came together in Leeds, England. We were delighted and very honoured to be joined by Dr David Koolen (after whom the syndrome is named, along with fellow geneticist Dr Bert de Vries) and his PhD student colleague, Katrin Linda, who both came in from the Netherlands. Having had a relaxed Friday evening which was a great chance to get to know friends old and new, the study weekend got into full swing on Saturday morning. The ‘Kool Club’ opened at 9, with childcare and lots of activities for the children and affected adults alike, including face painting, a chill out space and a dance workshop. This meant that parents were able to relax and listen to the presentations safe in the knowledge that their young people were being well cared for.

The morning session was taken up with presentations from Dr Koolen and Katrin Linda.

What causes Koolen-de Vries Syndrome and how was it discovered? Dr Koolen began with an overview of KDVS, explaining how was it discovered?

Some genetic syndromes, for example Angelman Syndrome and Prader-Willi Syndrome were first recognised due to similar physical characteristics among those affected, by facial features. However, KDVS was recognised by its genetic basis first, and then by the physical characterisation (a ‘genome-first characterisation’ as Dr Koolen put it). There are now in excess of 500 known cases of Koolen-de Vries Syndrome in the UK, Europe, the USA and Australia, with an estimated frequency of 1 in 16,000 newborn babies. Dr Koolen went on to say that is estimated that 1 in 2,000 children with global developmental delay have KDVS, most due to the deletion in 17q21.31. Ten-20 children with KDVS are known to have the KANSL1 mutation. KDVS is a multi-system disorder, with possible symptoms including hearing, vision, neurological and skin conditions, although not all are present in all children.

Children have a wide range of abilities, although the size of the deletion is not identical between children and Dr Koolen feels that the degree of

Q&A with Dr Koolen

To round-off the day, there was a short question and answer session in which Dr Koolen took some questions. A discussion point was whether regular heart and kidney scans are necessary for those with KDVS. Dr Koolen felt that it is important to carry out the relevant checks when a diagnosis is first made but that if no structural anomalies are found at that time there seems little point in having regular heart scans. He did not feel an annual check would be necessary. This led to a question about checks for epileptic episodes and Dr Koolen’s view was that it is important that parents are educated about the signs to look for when thinking about potential epilepsy so that they can then discuss with their child’s paediatrician.

The next question was from a parent who had noticed a ‘dimple’ at the base of their child’s spine. Dr Koolen said that it would be wise for paediatricians to investigate any potential issues with the spine and裡 the dimple that the parent had noticed. Dr Koolen felt that doctors would want to investigate whether the spine had closed properly at that point. In response to other questions, Dr Koolen said that regular eye checks for those with KDVS are important to

Koolen and his colleague Katrin had a family picnic in the grounds of Temple Newsam near Leeds. The weather was glorious and it was a lovely way for families to meet and spend some time together before heading home.

Craig Mitchell, COO of Unique said, “It was fantastic to see so many families and their very special children at the event and a very humbling experience. We are very grateful to Awards for All, part of the Big Lottery fund, for providing Unique with the funding for this event, to Mandy Hazelgrave for her tireless efforts to organise it and also to the families who helped to fundraise to make it a reality.”

A very special weekend was had and we hope that the children and families involved came away with a better understanding of the condition and each other. We are very grateful for the time and effort put in by Dr Koolen and Katrin Linda, and also to the families who shared their stories and experiences with us.

On the Sunday some of the families, along with Dr Koolen and Craig Newsam near Leeds. The weather was glorious and it was a lovely way for families to meet and spend some time together before heading home.

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characterised by intense brain activity and dreaming, our cerebral cortex (REM) It occurs several times during the second half of the night’s sleep, but comprises the smallest portion of our sleep cycle and involves an inability to use muscles, although we can use the diaphragm to breathe and eye muscles. Parents of children with KDVS report that night waking or early waking (ie too early!) as significant issues. Claire explained that we all wake through the night but don’t all have an ability to get back into the next sleep cycle. When we wake up and then go back to sleep, we don’t go back into deep sleep but more into a REM pattern.

What do you want to change?
When working with families, Claire asks parents: what do you want to change about your child’s sleep? Writing this down can help to focus on the problem - sleep is an issue that affects the whole household, including parents and siblings. There are four common sleep problems: difficulty settling, night waking, difficulty settling alone and early rising. If the issue is around difficulty settling, think about whether the child’s bedroom is suitable. Are the colours you have used on the walls too bright? It has been found that the blue is the most stimulating colour, along with green. In fact, blue light tells your brain that it is daytime so actually suppresses the melatonin produced. The red spectrum of colours don’t stimulate the brain in the same way and therefore allow the melatonin to work. Also ask whether there are there too many toys in the room? Take them out if there are or put them away into cupboards or boxes. Does the child have a bright night light? Are they ever stimulated in their bedroom? You might want to use blackout blinds to reduce light coming in, in particular during summer time. Think about their bedtime routine and whether they are calm when they go to bed or are they excited? Try to put them to bed when they are tired, even if it means doing so half an hour or an hour later. This may help reduce the time taken to settle and you can then gradually bring the time forward. Also think about whether their association with their bedroom with toys and playing. You might want to reinforce the bedtime routine by using visual timetables, something that dovetailed with what Nicki and Ben had mentioned earlier. The routine should take no more than one hour and a structured routine is very important. Do calm activities during this hour, switch devices like tablets off, give them a relaxing bath, maybe a hand or foot massage and then put them to bed in a calm, quiet way, making sure the room is dark. It’s worth noting that chocolate for example contains caffeine which is a stimulant and can remain in the body for up to 6 hours so avoid this close to bedtime.

Communication seems to be a prime concern, with parents frequently asking: does speech always arrive? He reviewed a study of 45 children (mean age 2 to 3 years old, and 35 children who had studied [their ‘in-house data’], had remained non-verbal, after being diagnosed with KDVS that this was a snapshot and that some children speak by the age of 5 years, some later on. Typically, first words are delayed but usually come between the ages of 18 months to 3 years or later. All those studies have expressive speech delay. Those with KDVS have a mixture of apraxia and dysarthria, though once language develops so children are able to catch up quite well.

Data from GenIDA shows that around 30% do not speak, and it is important to reflect that most of the data is about young children with and age and increasing number do begin to speak. In adulthood around 70% are able to read. One Mum reported that her son can express many more wishes through gestures than being non-verbal but using AAC (Augmentative and Alternative Communication) methods.

Behaviour was the next question Dr Koolen addressed. In 45 children studied in a non-longitudinal analysis 57% had behavioural/neuropsychiatric problems. Issues included Autism and ADHD. Occasional data in GenIDA, 70% have behavioural problems, with examples including repetitive behavior, hyperactivity, anxiety, phobias, hypervigilance and attention deficit. Epilepsy is another concern and Dr Koolen referenced a study undertaken by Ken Myers in Australia. Seizures were seen in approximately 50% of children (mean age 2 to 3 years), with a median onset of 3.5 years of age. The majority had reflex epilepsy but some were tricky to treat, with focal seizures the most frequent. There are usually prominent autonomic features. In 21 patients, the seizures were prolonged and hard to treat and 13/31 of these had structural anomalies of the brain including absence of the corpus callosum (ACC) and defects of the hippocampus. Visual Impairments such as strabismus (present in 41% of those studied) and hypermetropia (in 38%), as well as myopia and astigmatism are also relatively common, as is cerebral visual impairment in which the brain doesn’t process the stimulus. Another issue Dr Koolen felt parents should be aware of is Melanoma. He said that 18% of children studied were found to have factors that can affect their skin. This suggests a potentially increased risk of developing melanoma. He cautioned that most males never cause a problem but that someone with a high number is at greater risk and should be monitored on an ongoing basis. Other ectodermal problems also feature in 60% of people with KDVS, for example brittle nails, skin pigmentation and hair and teeth issues. Parents had also asked questions about their child’s weight. Most children seem to be slightly shorter than the average for their age and a lower weight, although usually still within the normal, expected range. Most children are very small and have grown hormone deficiency but in general Dr Koolen said that not being a significant problem.

Musculoskeletal problems such as hyper laxility, scoliosis, flat foot and myopia were also a feature though and more than 40% of children have some degree of joint laxity. Other, less frequent issues include the child having an abnormally-shaped skull (such as dolichocephaly, trigonocephaly, brachycephaly or scaphocephaly) a metopic ridge, bitemporal narrowing, gut issues and tooth grinding. The final question was about whether KDVS can currently be recognised during pregnancy. Dr Koolen explained that yes, it is possible to carry out a test in an amniocentesis sample that will detect the 17q21.31 deletion. He said that having a positive result for KDVS is a chance of future siblings also being affected is very low, at less than 1%, so the risks to the family are minimal. The amniocentesis need to be weighed up very carefully. Cases known to date are de novo mutations (inheritance from either parent) and pre-natal testing can be done but you should discuss and carefully consider the risks associated with this.

Dr Koolen was also asked about any direct link between parents having an inversion in 17q21.31 and their children having a deletion or duplication of this segment of chromosome. He replied that 40% of the general population carry an inversion in 17q21.31 but only a tiny percentage of the population have KDVS. Therefore he said if you do not carry the inversion it is not possible to have a child with KDVS but if you do carry the inversion then the risk is only an extremely low chance of having a child with KDVS.

Dr Koolen concluded by saying that KDVS is not caused by the parents inheriting something you do something during pregnancy or a particular behaviour, it is just something that happens in nature.

KANS I and Koolen-de Vries Syndrome
After a break for coffee and a chance to talk to other parents, Katrin Linda, a PhD student working with Dr Koolen in Nijmegen, Holland, took over to talk about the KANS I gene and why it is important to know about its function. She picked up on what Dr Koolen had said earlier on, that KANS I haplinsufficiency (lacking one copy of the gene) causes KDVS. Knowing and understanding the role this gene plays could help to treat specific symptoms and enable development of more specific and more effective drugs.

KANS I is part of the ‘non-specific lethal complex’ (NSL). It is needed as part of the mechanism to open up the protein (histone)-DNA complex in tightly coiled chromatin. By doing this the genes on the DNA, become more accessible in the first stage of gene expression / DNA transcription. The loss of one copy of the KANS I gene means this ‘opening up’ process does not work as well and the DNA and genes are less open to being expressed.

Using Animals and In vitro Models to study KDVS
Katrin then went on to describe some very complicated research techniques and first talked about using specific animals to model KDVS, beginning with the fruit fly, which has a gene called Wah, which is similar to KANS I. Studies by Lone et al, 2010 and Koolen et al 2012, had...
Communication books, choice boards, enabling the keep language simple: use follow the child’s lead

 Researchers into the syndrome can be tested. Indeed, a recent which different drug therapies (neurons) to provide a model turned into brain cells of animals in research. For body and that avoids the use possible in the whole human research to be undertaken on body cell. This enables

Dr. Koel and others, it’s known that help KDVS there is generally late development of first words and this usually happens between the ages of 18 months and 3 years, sometimes later. Children tend to follow a normal but delayed pattern of language development. There may be some discrepancy between comprehension and expressive language, with comprehension more advanced. In terms of speech development in those with KDVS, it matters to low language skill remains a long way off and that a large deletion such as that seen in KDVS involves loss of not just one gene but a large segment of genetic material involving six genes, including the critical KANSL1 gene. It affected children as another way of furthering this type of research into the syndrome.

Immunocytochemistry can be used to look at different building blocks for cell (different structural proteins). Using such immunocytochemical models, the properties of the dendrites of the NSL complex can be assessed and then different test conditions can be used to try to reverse the effect of the KANSL1 gene. Katrin explained that is is even possible to use microelectrode arrays (MEAs) which are little electrodes in the culture dish which can record the electrical activity of isolated neurons. These measurements can be done at different time points during neuronal cell development, making it possible to screen different drugs in the culture dish to observe their effects. Using this method, it could be seen that in normal healthy cells neuronal communication was fine but in KDVS neurons communication was disrupted. When looking at normal cells versus those with the KANSL1 mutation, it is possible to observe at what point in the cell’s development things go wrong.

Katrin concluded her presentation by answering a question raised about gene editing techniques such as CRISPR/Cas9. In mammalian cells these techniques can be used to target specific DNA regions of interest. When DNA is cut, there are mechanisms in place to repair it and it may be possible to correct a genetic mutation, for example using bacteria which does not contain the mutation. This is a potential way that single gene disorders could be treated in the future, although Katrin emphasised that remains a long way off and that a large deletion such as that seen in KDVS involves loss of not just one gene but a large segment of genetic material involving six genes, including the critical KANSL1 gene. It affected children as another way of furthering this type of research into the syndrome.

Immune response studies are not always the same. CRISPR/Cas9 does though allow people to examine the effects of a lack of the KANSL1 gene by creating a mutation in the single KANSL1 gene. The Kool Club closed for lunch to give the staff a well-earned break and all the young people were excited to tell everyone what they had been doing during the morning session. There were lots of painted faces and even some painted arm’s on display (and clothing too, though we’re not sure that was intentional! With all refreshed, the young people people went back to the Kool Club and parents returned for the afternoon workshop sessions.

Speech and Language Workshop
The first of the afternoon workshops was led by Nicki Arkel and Ben Bolton from Speech and Language and the Stammering Centre in service at Leeds Community Healthcare NHS Trust. Using research undertaken by Dr Koel and others, it’s known that help KDVS there is generally late development of first words and this usually happens between the ages of 18 months and 3 years, sometimes later. Children tend to follow a normal but delayed pattern of language development. There may be some discrepancy between comprehension and expressive language, with comprehension more advanced. In terms of speech development in those with KDVS, it matters to low language skill remains a long way off and that a large deletion such as that seen in KDVS involves loss of not just one gene but a large segment of genetic material involving six genes, including the critical KANSL1 gene. It affected children as another way of furthering this type of research into the syndrome.

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