Pallister Killian syndrome

***Unique* hosted an international study weekend for families with a child with Pallister Killian syndrome in Oxford, United Kingdom in October 2010. The meeting brought together families from Romania, Italy, the Netherlands, the USA and the Channel Islands as well as the United Kingdom.**

***Unique's* Pallister Killian weekend was the fifth and last in a series of disorder-specific weekends, supported financially by Jeans for Genes and the Grocers' Charity.**

Natural history of Pallister Killian syndrome

Dr Moira Blyth, consultant in clinical genetics for the Yorkshire Genetics Service, told a family audience for the first time about her recent survey of people with Pallister Killian syndrome.

In 1977 a Dr Pallister reported in the medical literature an adult with a learning disability and no obvious diagnosis. Four years later, a Dr Teschler-Nicola and a Dr Killian described a child, again with an unidentified learning disability. We now know that both have what we now call Pallister Killian syndrome. In the early literature it has different names: Killian/Pallister mosaic syndrome, Teschler Nicola Killian syndrome, but longer term we have stuck with Pallister Killian.

Pallister Killian is mosaic tetrasomy 12p. If you look at a normal cell you have 46 chromosomes. A child with Pallister Killian has some normal cells and some with a little structure called an isochromosome that consists of the short arm of chromosome 12 [12p] repeated either side of the centromere. In some of their cells, the child has four copies of 12p.

For my survey, I looked first at every published report of someone born alive with Pallister Killian: only 102 in the entire medical literature. Of these, 25 died within the first month of life. Beyond the age of 10, only 16 people have ever been reported. So answering the question 'What happens with the older kids?' is very hard.

I looked for everyone I could contact in Britain with Pallister Killian and got 22 families. The oldest patient I saw was 31 and most were pre-school. There was a relative lack of girls. There's no reason why there should be more boys but there does seem to be.

I looked then at babies diagnosed in pregnancy who were either miscarriages or the family terminated the pregnancy. Before 1990, there were only five live born babies and five terminations, while in 2005–2009 there were 20 terminations and 19 live births. I do not believe for a minute that Pallister Killian is getting that much more common: I am sure that we are getting a lot better at detecting it. Also, some laboratories have changed recently to testing any baby with a diaphragmatic hernia for Pallister Killian.

How many are there?

One question many families in the study asked me was 'How many are there?' I can now say that when I did the study in 2009, there were 36 people alive in Great Britain with Pallister Killian. That gives you a population frequency of 0.6 cases per million or, put another way, one person with PKS for every 1.63 million of the British population. In 2005–2009, the birth prevalence in Britain was 5.2 children with Pallister Killian per million live births, or one newborn baby with PKS per 192,000 live deliveries – and that is still an underestimate.

For whatever reason, PKS has turned out to be more common in males: from my total numbers 39 were male and 16 female – which at a probability value of p=0 .005 is statistically significant. An important bit for families is that there has never been a reported recurrence of Pallister Killian within a family, and that includes terminations. So the risk to any couple with a child with PKS of having more children with PKS should be no greater than the population risk. For reassurance, though, any family in Britain would be offered prenatal testing. For patients' siblings having children, there is no reason to think the risk would be any higher than the general population. But if a child with Pallister Killian – obviously one with the milder picture – has children, the risk is somewhere between zero and 50%. One's feeling is that it is closer to zero because an embryo who inherited the isochromosome and had tetrasomy 12p in all cells of the body would presumably not survive, but that is a 'presumably.' If it came to it, we would offer prenatal testing for reassurance until we know more.

So far we have not been able to explain how or when the isochromosome develops, whether it is in an egg or a sperm or whether it happens just after fertilisation once the baby is a few cells.

When do people die?

The second big question during the study was when do people die and what do they die of? Using British data we were able to identify eight who had died. One was a baby born at 21 weeks who died of prematurity on the first day of life; two children died at 4, one at 10, one adult at 20 and two at 38. One was an unexpected death in epilepsy; one died of aspiration, which is very common in children with something like Pallister Killian where the muscles are very weak. The other four died of some form of respiratory infection but for most, we only know what was on the death certificates. Sometimes 'pneumonia' can be a way of explaining a natural death that you cannot completely explain; sometimes it is a child with a very severe picture whose parents might choose not to go for intensive care; or these may be children who had overwhelming infections; we cannot tell.

Development

Looking at development, in the medical literature there are just four people with either a mild or moderate learning disability; the rest have a severe or profound picture and so are not expected to walk or talk. If you meet some of the people with Pallister Killian who are here, you will realise that is definitely not true: it is very variable.

Of the 12 school-age children I saw, three were in mainstream schooling. Quite a lot do have significant delay and in some it is severe or profound. Walking is something that people often ask about: we class walking before 18 months as normal. Of my group, one walked at

16 months and the oldest one at 8 years. Nearly a third were walking by their third birthday and about half by their fourth birthday; three children of 10 or 11 were not walking.

In terms of development, we looked at gross motor skills [walking, running, jumping etc]; fine motor skills [hand movement]; language; and personal and social skills [feeding yourself, using a knife and fork; dressing]. I saw one four-month-old who was entirely normal, some children who were very significantly delayed and others who were functioning at almost their actual age. One noticeable thing is that normally children's developmental level was broadly the same in all the areas we looked at. So we didn't see children whose gross motor skills were really good and whose fine motor skills or language was really bad. That said, the oldest patient I saw was happily walking around the room but did not say a word – but she had not developed the skills like running, jumping or hopping that you expect two or three year olds to start developing.

In the ones over 5, again we have got some who have done really well but another group who are really not doing anything much.

Answering a question from a parent, Dr Blyth explained that the language assessment measured speech ability rather than ability to communicate, so it would underestimate the abilities of someone who communicates, for example, by signing.

Seizures

Looking at the features of the syndrome, a lot of children have seizures [fits]. These started either between 6 months and three years old or between 8 and 11. No-one started fitting between 3 and 8, but that may simply be due to small numbers or to when it was diagnosed. Some children have absence seizures, where they do not seem to be there for a minute, and then progress to other forms of seizure. A lot of parents said the children have myoclonic seizures and I thought that might be a clue that Pallister Killian is having some different effect from other chromosomal disorders. We had three babies already fitting before their first birthday and five before their second. By their fourth birthday there are 11, more than half, and by 13, only one child is not having seizures. Looking in the medical literature there are reports of babies fitting within the first month of life and also of people who had their first seizures as adults so you have a massive spectrum.

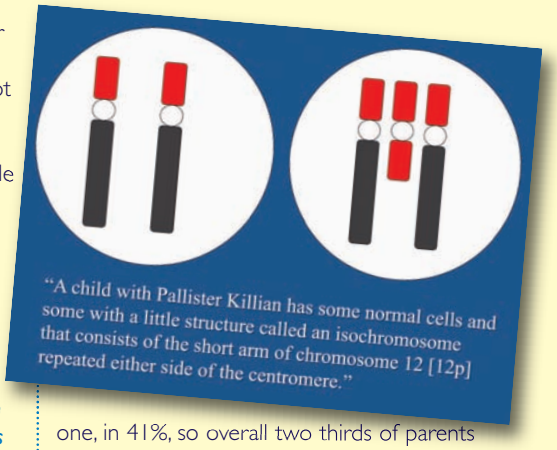
Answering questions, Dr Blyth repeated that some people only had their first seizure as adults and said she came across no-one who completely stopped having seizures. That said, she admitted that, unless antiepileptic medication was withdrawn when seizures were believed to be controlled, it was not possible to be certain that seizures would continue without it, but that epilepsy generally lasts.

'Common' features

Looking at other common features, nothing happens in 100% of people and lots of 'common' features do not happen even in 50%, which may be a reason it is difficult to diagnose Pallister Killian in children without the characteristic facial picture. Starting in pregnancy, polyhydramnios [extra fluid round about the baby] was fairly frequent [17%] in my group, although mothers who had it mildly late in pregnancy may never have been told.

Now, looking at birth weights, the medical literature and summaries of PKS tell you that babies with Pallister Killian are supposed to big – but they aren't. Most of the birth weights in my group were within the normal ranges – only 13% of mine were at the top of the birth weight scale and none were off it. It is only in the group as a whole that you see any increase in comparison to the general population.

Floppy babies [hypotonia] were very common [77%], from parental recall. When I examined the children, in half [52%] the muscle tone was still not as good as you would expect. More than a quarter [27%] of parents really felt their newborn baby had difficulties feeding. They needed additional help or multiple goes at different types of teat before they started feeding, though only a couple needed artificial feeding. Feeding was still an issue, but less of



"A child with Pallister Killian has some normal cells and some with a little structure called an isochromosome that consists of the short arm of chromosome 12 [12p] repeated either side of the centromere."

one, in 41%, so overall two thirds of parents said they had some difficulties with feeding. Most of this is because babies are floppier than normal, so the tone in the mouth and throat and the ability to use the tongue is reduced. They do tend to outgrow this with age.

In this group there were not many birth defects [congenital malformations]. Cleft palate occurred in two babies [9%], one a 'proper' cleft palate, right across the roof of the mouth, the other a submucous cleft palate where the skin has grown over the roof of the mouth but the bone above is not sealed together correctly. Split uvula [bifid uvula] is reported fairly commonly, although I did not look into throats unless the patient could cooperate.

Congenital dislocation of the hips, where the ball of the femur [thigh bone] is not correctly positioned in the hip joint, is fairly common [14%]. Based on children where a report from a chest X-ray was still available, a quarter only have 11 pairs of ribs instead of the normal 12, compared with about 5% of the general population.

Umbilical hernias [around the belly button] were found in about a quarter [23%], compared with 2–5% in the general population. Inguinal hernias [in the groin] are more common in boys and two boys I saw had them. That works out as 9% of the Pallister Killian group and about 14% of boys with Pallister Killian, significantly higher than the general risk of under 1%.

A lot of parents [55%] said their child definitely had a delay in the closure of the fontanelle [the soft spot on top of the head] and this figure may actually be higher. A very similar number [57%] had delay in the teeth coming in. Medically, the two go together as they are due to a delay in the bone age.

Often a good clue to a mosaic disorder is that people have patches of paler skin, darker skin or both, and sometimes stripes. Some of these children have wavy stripes on the top of the chest and abdomen and down the back and linear streaks on the limbs. You might find that with a cohort of those with the condition rather than those in whom the diagnosis has been made the number would be lower, but I found this in 64%.

Additional nipples are very common according to the literature but most parents say they

know nothing about them. The human body has a nipple line that runs from under the arm through the normal nipple down onto the abdomen. Extra nipples tend to be very subtle, but 41% of my group had at least one. They are often very small and quite a lot of parents thought it was a birthmark.

The percentage of children with some hearing impairment seems surprising. In the medical literature, a little group have them, a few significantly. Of my group 32% had hearing aids and 77% had some hearing impairment. Do remember of course that glue ear is common in the general population and three of these PKS children had glue ear with grommets.

Nystagmus [the eyes wobble backwards and forwards], was seen in 14%. Another 14% had hypoplasia [poor growth] of the optic nerve which takes the vision from the eyes to the brain and this is likely to affect their ability to see or to process what they see.

Scoliosis [27%] is a bend in the spine and is much more common in children who are hypotonic [floppy]. Without the muscle tone to hold the back straight and well aligned, scoliosis can develop over time, although when professionals are aware of it and children are given wheelchairs with appropriate support, it is less significant. I could still straighten the child's back in quite a few children I saw, so this was a position they chose rather than any malformation of the back.

Nobody in my group had what we could call really significant or severe infections, but 55% of parents said they believed their child had more infections or more severe ones than children of a similar age. Again, this is likely to be due in part to hypotonia, so not having good muscle control in the lungs, not coughing up secretions with a cold, making these children more prone to getting chest infections. There may also be an increase in ear infections. As they get older and bigger and stronger, this does tail off.

One parent told me early on that their child does not sweat, so I added the question for most families and got 41% saying either their child does not sweat or they have markedly decreased sweating. I have no idea why this happens but it is clearly a feature of Pallister Killian and is giving some people significant problems.

Another oddity was spells of hyperventilation [breathing very fast] which I noticed in a child in an early interview. I found four [23%] who did this and of those, two also had spells of breath holding. There are various bits of the nervous system that control breathing and some genetic conditions like Rett and Angelman syndromes where children are prone to hyperventilation but they are not chromosomal ones. I do not know why children with Pallister Killian would be more prone to it.

In terms of behaviour, a quarter of the group [27%] said that their child had some autistic features – either the children desperately needed routine, or instead of playing with toys would put them into tidy lines. However, these children did not have full-blown autism, which is massively different from that.

We also have about a third [36%] saying that their child has some self-injurous behaviours, from banging heads on walls or floors, biting at hands or fingers or whacking themselves on the head. You do get this sort of behaviour in children with developmental delay and perhaps sometimes it is just because they feel something when they do it.

And I am sure a lot of you are thinking about sleeping problems. Half of the families I saw [50%] said they either have problems getting the child to sleep, waking up repeatedly in the night or deciding that four o' clock in the morning is a nice time to get up.

Now just taking the group detected antenatally who underwent termination of pregnancy, 36% had diaphragmatic hernias. In some cases, the fetus had a diaphragmatic hernia, they terminated the pregnancy and then had genetic testing. In others, the genetic testing was done during pregnancy and then the termination was carried out. That is 36% compared to 0% in the group I saw and in the medical literature diaphragmatic hernia is reported in around 60% in the first month of life. So I think this really shows us that with improvements in antenatal care and testing, people are having the diagnosis made earlier and children with these malformations are not being born.

We also have a 9% rate for heart malformations, significant defects that are potentially fatal. This again supports what is said in the older medical literature.

One feature that is supposed to be common is extra fingers or toes but we only found it in 4%, although the way the data are collected means this may be an under-representation.

Diagnosing PKS

Finally, we looked at where the diagnosis was made. Most children here will have had a skin biopsy to confirm the diagnosis and 82% of my

Questions

Q ***When our daughter was born 20 years ago, I had amniocentesis [amnio] but was told then that Pallister Killian could not be picked up. Has there been progress?***

A *There are lots of amniocenteses coming through confirming Pallister Killian.*

Q ***My Pallister Killian son is my older son, and I wanted prenatal testing for my younger son. I wanted CVS but was advised against it and to go to amniocentesis.***

A *First, the miscarriage risk for CVS is 1–2% and for amniocentesis more like 0.5%. Second, amnios these days seem to be picking up all the Pallister Killian babies whereas out of a very small number of CVSs, we know of 30% giving normal results and the baby turning out to have Pallister Killian.*

Q ***Why would an amnio be more correct than the CVS?***

A *Partly because an amnio is analysing fetal skin shed into the water around the baby whereas a CVS is a biopsy of the placenta. It may also be partly to do with the way the cells divide. We know that cells with the isochromosome do not divide as well when you provoke them as normal cells do. For CVSs you have to push the cells to divide, whereas in an amnio you have to push them less. Theoretically, you could have a false negative on an amnio because there are false negatives on skin biopsies – but we didn't see this happen.*

Q ***Are these percentages on CVS very different for other chromosomal abnormalities?***

A *Yes, because this is a mosaic disorder and not present in all cells. In other conditions there may be mosaicism in the placenta but not in the baby. In Pallister Killian, there may be mosaicism in the baby with a normal placenta, or there may be normal and abnormal parts of the placenta, so if you take the biopsy from the normal part you will not pick up any abnormal cells.*

group had a skin biopsy. In some instances the diagnosis had already been made on a mouth brush sample and the skin biopsy was for confirmation, in other cases the skin biopsy made the original diagnosis. I repeated the mouth brush sample on all the children I could and got a positive result in 75%. This means that 25% would not have been picked up if you only used this test for diagnosis.

We also tried array CGH testing, which gives a much more detailed picture of the chromosomes and is becoming the first-line test in quite a lot of genetic centres for any child with learning difficulties. I wanted to see whether an array CGH test diagnoses Pallister Killian or not. The answer was that only 17% of my group were positive so a negative result on array CGH does not in any way mean the child does not have Pallister Killian.

Finally, how accurate is antenatal testing? Amniocentesis at 16–18 weeks seems to have a good pick-up. But my data showed that out of 13 women who had chorionic villus sampling [CVS] in early pregnancy, four were given normal results but the child had Pallister Killian.

Treatment options for epilepsy – medication and indication for the ketogenic diet

Dr Christin Eltze, consultant paediatric neurologist at Great Ormond Street Hospital, talked to families about medication and other treatments.

I want to talk about the principles of antiepileptic drug [AED] treatment and what can be done if AEDs are not working. Normal brain function is quite complex and is carried out by nerve cells in the mantle of the brain, the cortex. In simple terms nerve cells communicate with each other using electrical impulses and work in networks to establish complex functions like language production and understanding, vision and motor function. During an epileptic seizure there is a sudden burst of abnormal electrical activity which leads to a transient brain dysfunction. You can see patients' behaviour change or patients themselves may feel something. What you see depends very much where in the brain this dysfunction occurs.

We divide seizure types into two main categories. In *focal* seizures, earlier called partial or complex partial seizures, the abnormal electrical activity mainly starts within one side (hemisphere) of the brain. In *generalised* seizures, the abnormal activity starts on both sides of the brain.

Questions

Q *How do you describe an absence seizure?*

A *In absence seizures, you see a specific feature on the EEG [electroencephalogram] and a very brief 'switching off', stopping, staring, eyelid flickering or lip smacking. They often last less than half a minute and can occasionally be quite frequent.*

One epileptic seizure does not constitute epilepsy. In epilepsy, seizures are recurrent. Many conditions and disorders manifest with epilepsy and chromosomal abnormalities are only one of these. There are also events, medically termed paroxysmal events, which occur intermittently but are unrelated to epilepsy, such as fainting. Sleep-related events like night terrors must also be distinguished from epilepsy. Description of the events from witnesses such as parents helps us decide if an attack is epileptic or non-epileptic and additional information from home videos is particularly useful. The EEG recording that we make between attacks can help, but a normal recording does not rule out epilepsy. An attack during a video recording with EEG (video-EEG) can confirm that the event is a manifestation of epileptiform activity.

Currently we do not know what causes epileptic seizures in Pallister Killian but certain seizure types are more common. The literature gives very little information on seizure types but I noticed five reports of patients who presented with late-onset epileptic spasms (17 months to 9 years of age). In most, epileptic spasms were difficult to control with antiepileptic medication. In young children epileptic spasms often manifest with a brief (1–2 seconds) sudden flexion of the neck and trunk with sidewards movements of the arms, often recurring repeatedly over a period of time (cluster of spasms). Epileptic spasms can be subtle and might be overlooked. A myoclonic seizure is a sudden jerk-like movement, usually briefer than a spasm, that may involve the limbs (one side of the body or both, often involving arms), neck or trunk. Some episodes described by parents as 'jerks' turn out on video-EEG to be epileptic spasms.

Questions

Q *What are the consequences of spasms that are not picked up early?*

A *The impact on cognitive outcome of a delay in treating epileptic spasms with onset in very early childhood is subject to research and is debated among paediatric neurologists. Some data in children with early-onset epileptic spasms (particularly with no underlying cause), suggest that the cognitive outcomes are less favourable when treatment is delayed. But the underlying cause probably plays a big role and at the moment we have too little data to confirm that early treatment will improve cognitive outcome in all cases, independent of the underlying cause. Our current practice in paediatric neurology is to treat epileptic spasms in very young children early (under the age of 2 years), promptly (as soon as these are recognised) and rigorously.*

Q *What kind of test can I request? My daughter is 12 and sometimes gets these jerks.*

A *No single test unfortunately makes the diagnosis. Your doctor, paediatrician or paediatric neurologist can decide, based on a home video and clinical information, what further investigations are needed. If they are really frequent, an EEG or video-EEG would be helpful.*

Treatment and side effects

The first aim is to improve seizure control: overall a quarter of children have epilepsy that is resistant to AEDs. Drug resistance is more prevalent when there is a known cause such as an underlying brain abnormality, an abnormal neurological examination or if the seizures started very early in life.

Choice of AED is guided by seizure and epilepsy type. For example, in cases with absence seizures we would consider starting sodium valproate, ethosuximide or lamotrigine and would avoid use of carbamazepine or vigabatrin because these can make absences worse. We also try to avoid carbamazepine and vigabatrin for myoclonic seizures because they can make them worse. You have to go through this with your doctor.

Consideration of side effects is very important. Phenytoin and phenobarbitone were very effective drugs but their side effects are worse than many of the newer antiepileptic drugs and we use them now as third choice when other AEDs fail or for short-term treatment in emergencies. To minimise side effects, we aim for as few AEDs as possible, one or two if possible and only exceptionally three. Very infrequent seizures probably do not warrant taking an AED every day: discuss this with your paediatrician or paediatric neurologist. And discuss treatment goals: if seizure freedom is not achievable, drug treatment should be targeted at seizures with the greatest impact on the child's quality of life.

Side effects commonly include sedation, tiredness, dizziness and unsteadiness, particularly when AEDs are initiated, so we usually start with a low dose, increasing it gradually. The biggest problem for patients with difficult epilepsy is that some AEDs, for example sodium valproate, may exacerbate behaviour difficulties. Concentration problems, loss or increase of appetite and nausea and vomiting can be a problem with some AEDs. Allergic reactions, especially a skin rash, can occur more frequently with carbamazepine, lamotrigine or phenytoin. Severe life-threatening reactions are rare but can affect skin, liver or even the bone marrow. Long term AED treatment can be associated with hormone disturbances and thyroid function may have to be monitored. There is an impact on bone mineralisation because some AEDs interfere with vitamin D metabolism. And some AEDs may cause increased phosphate leakage through the kidneys.

Some children have seizures that continue after five minutes and evolve into status epilepticus; others experience periods of very frequent seizures that interfere with their consciousness and functioning. An emergency régime for these kinds of seizures is important: we use benzodiazepines: buccal midazolam or rectal diazepam.

If AEDs fail

There are at least 10 AEDs available and you can work your way through them. But other options to explore include the ketogenic diet. This is a high-fat, carbohydrate-restricted diet which aims to simulate the biochemical changes of starvation in the body. During starvation, the body breaks down fatty acids in the liver and builds up ketones which are used as a source of energy by the brain and muscles. Paediatricians in the 1920s noted that when children with epilepsy were unwell and unable to eat, they appeared to have fewer seizures. Physicians then devised fat-rich, low-carbohydrate diets that forced the body to produce ketones: some patients with epilepsy became seizure-free and others showed marked improvement. The classical ketogenic diet was developed.

In our normal diet, a little over half the energy comes from carbohydrate and 20–25% from fat. In the classical ketogenic diet we increase the fat to 90%, reducing the combined carbohydrate and protein proportion to 10%. This means that a child has to follow a very strict diet with a calculated meal plan. The other form is the medium chain triglyceride [MCT] diet, derived from the observation that MCTs make the body produce more ketones. On the MCT diet, 40–60% of daily calories are given as MCT oil or as Liquigen, a special formula. This diet has 75% fat and patients are allowed 15–20% of calories from carbohydrate and protein. Matthew's Friends **[www.matthewsfriends.org]** is one of the charities which help parents, particularly with recipes. The modified Atkins diet is a high fat diet with restricted carbohydrate intake but unlimited protein allowance.

Questions

Q ***Surely ketones are poisonous? Isn't it dangerous to induce them?***

A *When I am unwell and do not eat for two days, my body produces ketones which provide energy but my body does not poison itself. They are a natural response to starvation. Occasionally the ketone level may become too high in which case a child may show symptoms. These usually improve if some carbohydrate is given, usually as a small amount of fruit juice, to reduce ketone production. If a child on the ketogenic diet is unwell, the ketone level may become too high and worsen the condition of the child. We instruct the parents/carers of our children on the ketogenic diet how to manage children when they are ill and especially to recognise the signs when their children become unwell, when they should be brought to a doctor or hospital for assessment and treatment without delay.*

We consider the diet firstly with patients who have drug-resistant epilepsy who have trialled several AEDs but still have seizures with a significant impact on their quality of life, also with patients who tolerate AEDs very poorly and in some rare metabolic disorders. Some conditions, generally ones that cause low blood sugar or high lipids and some metabolic disorders are worsened by the ketogenic diet. There is also no point in starting any child with massive feeding or significant swallowing problems on the ketogenic diet without addressing these first. The diet can be considered for children who are fed through a gastrostomy. There is a risk of vitamin and mineral deficiencies so all our patients are on supplements and have regular blood tests. We also monitor weight and growth.

But does the ketogenic diet work? A systematic review of studies *[Pediatric Neurology 2006 Vol 35 pp 1–5]* reported that after six months, 16% of 972 patients became seizure-free and 33% had more than 50% seizure reduction. I don't know how many patients had less than 50% seizure reduction. Forty to 50% of children who remain on the ketogenic diet for 6 months experience more than 50% seizure reduction.

Trials at Great Ormond Street Hospital *[Lancet Neurology 2008 Vol 7(6) pp 500–6; Epilepsia 2009 Vol 50(5) pp 1109–17]* show that both the ketogenic and MCT diets appear to work. But side effects can be a problem, particularly in the beginning, with vomiting, diarrhoea, constipation, hunger and compliance issues. Both diets have similar side effects although vomiting was a little more common on the classical diet. Relatively few patients dropped out because of side effects. Side effects such as constipation can usually be managed by adding

fibre and using laxatives. We give our patients information on what to do if they have other side effects at the beginning such as low blood sugar or excessive ketosis, which is monitored by carers. A proportion of patients may also present with kidney stones. The risk of this happening can be minimised by alkalising the urine (using polycitrate supplements). Hyperlipidaemia is a long-term problem, but should be balanced against the risk of uncontrolled epilepsy. Weight and growth must be monitored. Other long-term side effects include decreased bone density (because of impaired bone mineralisation on the ketogenic diet) with risk of fractures. Cardiac problems have been reported in very rare cases.

Before starting the diet, we assess patients in detail, looking for any contraindications. We then set goals, aiming for seizure reduction – only a small proportion of patients become seizure free – and reduction of antiepileptic medication. There is little evidence that the ketogenic diet directly improves cognitive or motor function, though it may do so indirectly by reducing seizure burden and reduction of AEDs (reduction of AED side effects). Some teams start the diet in hospital, others like us as outpatients. After three months we usually establish whether it has worked. Seizure diaries can be very helpful when comparing seizure control before starting and while on the diet. If it works, we carry on, reviewing patients six-monthly, but after two years we usually try to reduce the fat ratio to see if the epilepsy has progressed and the ketogenic diet may no longer be necessary to control seizures.

Data show that patients drop out over time, either because the diet is not working or there are difficulties with compliance. After two years only 20% may still be on the diet. But there are observational data suggesting that seizure control remains improved 4 years after starting on the diet in a proportion of patients – even after coming of the diet.

You need a team for the ketogenic diet: a specifically trained dietician, a paediatric neurologist or experienced paediatrician and perhaps a clinical nurse specialist to liaise with your local paediatric team if problems occur.

Vagus nerve stimulation [VNS]

VNS therapy, another non-pharmacological treatment, is based on repeated electrical stimulation of the left vagus nerve by a pulse generator device. It can abort a seizure and may increasingly prevent seizures. Other benefits can include positive effects on mood, alertness and behaviour.

An electrical generator device is implanted under the skin on the chest or armpit; an electrical lead goes under the skin up to the neck where it is then coiled around the vagus nerve. The device on the chest is programmed and the pulse sequence, frequency and the strength can be changed or stopped with a little swipeable magnet. It's unclear how it works but we know that the vagus nerve is connected to many areas in the brain including the locus coeruleus and there may be metabolic changes in the thalamus, brainstem or elsewhere in the brain that raise the seizure threshold.

Studies have shown that one third of implanted patients have at least 50% seizure reduction and in some newer studies including children a half do. In one trial, a third of patients had some response but less than 50% improvement and a third had no response. The optimum effect took a few months to 1–2 years to show.

The vagus nerve is responsible for the function of the voice and the swallowing muscles so a child with severe swallowing problems is usually not suitable for VNS treatment. Side effects include a hoarse voice, cough and throat tickling but decrease over time. You can remove a VNS device that is not working but the wire along the vagus nerve is difficult to remove and usually stays in place, so children with a VNS device cannot go through a normal MRI scan because the wires can heat up and cause damage. There are special MRI scanners which only cover the head area and these would be suitable for such patients.

In conclusion, diagnosing epilepsy correctly is important and AEDs are usually the first option. We aim for the fewest AEDs with the least side effects and you should set realistic goals. Explore non-pharmacological treatments early because they may take time to implement. The ketogenic diet works for some but needs a dietician: physician team, significantly changes lifestyle and may be hard for some families and children to follow.

Families' Questions

CE = *Dr Christin Eltze*
EH = *Emma Hyde*
ES = *Dr Eugen Strehle*
MB = *Dr Moira Blyth*
NL = *Nicola Lathey*
PE = *Pattie Everitt*

Epilepsy

Q ***How specific is epilepsy in Pallister Killian? Our local services have very little information.***

A *In general we assess patients with PKS like any other patient with epilepsy. We are collecting data but PKS is rare.* [CE]

Q ***What causes spasms after my son wakes up?***

A *You should consult your paediatrician or paediatric neurologist, because you cannot assume that you are seeing epileptic spasms. Reflux is a differential diagnosis and should be evaluated.* [CE]

Q ***A lot of seizure activity is sleep-related, nocturnal or as they wake.***

A *We commonly see epileptic spasms after waking. We are not certain what makes seizures more frequent in sleep but the brain may switch to a different state that we can see on the EEG.* [CE]

Q ***Are children having epileptic spasms conscious or unconscious?***

A *They are often very young, so we can only observe them. From my observation, some appear to be aware.* [CE]

Q ***During these episodes can they speak?***

A *You saw the little girl on the video who was playing, had the spasm and carried on immediately afterwards.* [CE]

Q ***The episodes are not particularly short, several minutes maybe.***

A *Episodes like that don't sound like seizures. Sometimes parents say that their child carries on, is aware or cries between spasms. Whether he is aware in the two seconds of the spasm, I don't know.* [CE]

Q ***Is it helpful to do an EEG during these episodes?***

A *Yes: video-EEG capturing these episodes would be very helpful and diagnostic. I would go through the history in great detail and assure myself that the episode has the characteristics of an epileptic spasm before considering AEDs. Some people are confident to make this decision based on the clinical signs and history whereas others want at least a baseline EEG. Most of my colleagues would like an EEG in waking and sleep to develop a better understanding.* [CE]

Q *My daughter has episodes in the night. We don't know if they are epilepsy or night terrors.*

A *Children can be admitted for overnight filming and EEGs. I don't think there's any other way to judge it.* [MB]

Melatonin for sleep

Q *Do you use melatonin?*

A *Melatonin is a natural hormone whose main job is to induce sleep. Some children with brain-related conditions may release it but at the wrong times or use it incorrectly. In the UK it's unlicensed, so is normally available through consultants. Melatonin can sometimes help with getting off to sleep, but very rarely helps with night waking. It works in some children, but not all.* [PE]

Q *Our daughter's been on melatonin for 9 years and we are wondering about taking her off it because she is very drowsy in the morning, though she is also on AEDs.*

A *There isn't enough research into the long term effects. Melatonin is often used short term to get a child into a sleep pattern. Children I have seen have normally come off it because it's no longer effective.* [PE]

Q *Could it be addictive?*

A *It doesn't seem to be. Compared to other sleep medications it has very few side effects. Some children become tolerant but that may be because they are getting older and bigger.* [PE]

Supplements

Q *My baby was very shut off from the world until we gave her supplements of aminoacids, iron, vitamin B, folic acid and DHA [an omega-3 fatty acid]. Within a week, she was more alert. When I stopped the vitamins, she regressed. When I gave them again, her attention improved. Her therapists and doctor who didn't know about the supplements remarked on her progress. I don't know if this is due to her normal development or the supplements.*

A *These are substances normally found in food; fish contains omega-3 fatty acids. The evidence is not very strong but they have been shown to help – though not cure – autism and ADHD [attention deficit hyperactivity disorder]. For chromosome disorders, there is really no evidence but at the recommended dose they should do no harm. Many parents say they see changes with food supplements but there is also the placebo effect: simply giving a pill can help a child to improve.* [ES]

There is no evidence but if you feel it's having a significant impact, then presumably it's doing no harm. I would be cautious with iron because you can give too much. [MB]

Pain threshold

Q *Our daughter won't tell us when she is in pain but she signs if she falls over and is bleeding. We suspect that she has a lot of pain and doesn't know how to manifest it. Did you come across this?*

A *Not specifically in the Pallister Killian group. It's fairly common in children with learning difficulties: whether they don't feel pain as we do or whether they don't express it, I can't tell you.* [MB]

*There are signs for pain in a particular area and a general sign for hurt. You could rôle play somebody falling over and say 'Ow! Ow' or 'Hurt' so she knows that should lead to getting help. Using puppets or social stories might help: look on the internet ['Social stories' at **www.autism.org.uk**].* [NL]

You are halfway there if she acknowledges pain when she sees blood. You could use fake blood to show 'Blood means pain and I need Mummy'. [EH]

Try plasters or magic bandages. One family mentioned delayed pain, 15–30 seconds after the event.. [Families]

Ear infections and ear wax

Q *Any advice for a child with narrow ear canals, constant ear infections and ear wax?*

A *Ear wax is normal; you shouldn't try to remove it. Most ear infections are caused by viruses and don't need antibiotics. If a child has a severe infection, the wax often melts and you perhaps have discharge. These are the instances when you need to give antibiotics. If you are worried about frequent ear infections, perhaps associated with glue ear, your child should see an ear, nose and throat specialist.* [ES]

Gallstones

Q *Gallstones: has my daughter's diet affected this and has anyone else had them?*

A *It's an isolated one from my point of view.* [MB]

Different types of gallstones can occur in any children. To my knowledge, it's not diet-related. In children, they are often not painful. [ES]

Cutting teeth

Q *Our son has had two huge symmetrical lumps on his lower jaw for a year, where the teeth don't cut through. The dentists have never seen this before. We don't know if it is painful. Have other families experienced this and how have they dealt with it?*

A *Sometimes you need to chew and stimulate the mouth: the Chewy Tube [available in the UK through **www.eg-training.co.uk** or from Kapitex at **www.kapitex.com**] might help or you can get a vibrating teether from Mothercare.* [NL]

Our son's teeth were slow to come through and two are fused; he was born with a bulge in one of the gums. Try a child's battery-operated toothbrush. [Families]

First steps

Q *At what age were children able to walk? Why do some not walk?*

A *The range I found was 16 months to 8 years. Some children are much more severely affected than others.* [MB]

Our physical therapist said that a child who starts walking after 3 will have a modified gait but before 3 can have a normal walk. Our daughter walked at 7: never give up. We used a wheeled toy dog. [Families]

Q *Is there any sign in early development to tell us whether our child will walk?*

A *No: it is individual. There are very severe ones who at 3 make no effort to sit and are the same at 13. The ones who were maybe sitting on their own at 18 months are more likely to walk later.* [MB]

Constipation

Q *Our son takes lactulose a few times a day but can still go 2–3 days without doing his number twos [poos] and is then in excruciating pain.*

A *Anything oral like lactulose gives our son stomach ache; we give him a Duphalac suppository [prescribed by the GP] every other day. Movicol. I use a natural remedy, one capsule of Oxy-Powder every morning with breakfast, recommended by a herbalist. Benefiber and Senokot. We inject warm water through a syringe, hold the child for a couple of minutes, then take him to the toilet. Warm water with sugar to drink before breakfast. No medicines but we help with a stick. Sometimes the reflex doesn't work so we scoop.* [Families]

Pallister Killian syndrome

Managing children who don't sweat

Q *How do you manage a child's inability to sweat and control their temperature?*

A *A fan that sprays water on the face.* [Family]

Cold feet

Q *My daughter always has cold feet though not hands, a normal colour. She has no underlying heart disease.*

A *Children with chromosomal disorders quite commonly have cold feet and it doesn't necessarily mean there is underlying heart disease. Always make sure her feet are wrapped up.* [ES]

Life expectancy

Q *What is the life expectancy and is this governed by the severity of the PKS?*

A *The data isn't available to give a very good answer. I'm sure that how badly they are affected will have a significant impact. But in my group, the child who had the sudden death in epilepsy was one of the milder ones. The oldest surviving one in the medical literature was 45.* [MB]

Different biopsies

Q *To diagnose our son, they took skin and muscle biopsies. The skin biopsy gave PKS. The muscle biopsy gave a mitochondrial disorder. Because both disorders are rare, 'they' skip the metabolic diagnosis.*

A *Without seeing the metabolic report, this is guesswork, but a lot of metabolic abnormalities on muscle biopsies are subtle. If you have a skin biopsy that 100% confirmed Pallister Killian, the question on the muscle biopsy report is: are those subtle abnormalities that don't add up to anything specific or has the child got two separate diagnoses?* [MB]

Skin

Q *Do PKS children have an increased risk of skin cancer?*

A *There is no evidence anywhere that children with Pallister Killian have an increased risk of any cancer. That said, you should assume that very pale skin patches are more likely to burn so if your child has any that will be sun-exposed, you should take more precautions.* [MB]

Before my son's diagnosis, we took him camping. I smothered him in sun cream and he got 'raspberry ripple' on his legs. We protect the areas that burn very easily with factor 50 sun cream as with any child but a little earlier in the season. [Family]

The darker skin has more melanocytes that make the tanning. Quite a few families said their child didn't seem to have any stripes until they took them to Majorca or wherever. [MB]

Dribbling

Q *What treatments are there for dribbling?*

A *As well as hyoscine patches, a medicine called glycopyrrolate can be given by mouth. Some children have had Botox injections into the salivary glands but this has to be done in a specialist centre.* [ES]

Our son has had the salivary ducts at the bottom of the mouth tied off so saliva still comes from the top of the mouth but not the bottom. This worked for us. My son outgrew dribbling around 6–8 years. [Families]

Puberty

Q *When do we expect puberty, what should we expect and how do we manage it?*

A *In my small group, puberty occurred at normal times.* [MB]

It is likely to be variable. In general in chromosome disorders puberty can be delayed, but can also start early. Periods can be difficult to manage in children with learning difficulties. Some paediatricians or paediatric endocrinologists recommend the contraceptive pill or an operation as a last resort. [ES]

Joint dislocations

Q *How can joint dislocations be reduced?*

A *Lots of Pallister Killian kids can dislocate their hips and legs and sit in any position when they are little without pain. The ones who are operated are usually those who are walking or expected to walk. The dislocated hip quite often doesn't bother the child and has been left. These are children who are more severe and are not trying to weight bear, so there's little point in putting them through an operation that's not going to help them.* [MB]

My son is due to be operated because his right hip is 70% dislocated and his left hip 50%. He weight bears and his hips are now starting to put his back out of line. [Family]

This report is dedicated to the memory of Josh Rayner and Edward McMahon.

This report includes the specific Pallister Killian and epilepsy presentations as well as families' questions. The slides from the other presentations are also available on the members-only part of the *Unique* website. These include: *Creating a 3D model of typical faces in Pallister-Killian syndrome* [Peter Hammond, Professor of Computational Biology, Institute of Child Health, London]; *Practical Strategies for Developing Communication Skills* [Nicola Lathey, speech and language therapist]; *Challenging Behaviour in Children with Special Needs* [Emma Hyde, Clinical Nurse Specialist]; *What is 'normal' development?* [Karen Sutherland, clinical psychologist in training; *The Child with a Chromosomal Disorder from a Paediatric Perspective* [Dr Eugen Strehle, paediatrician]; and *Cerebra Sleep Service* [Pattie Everitt, Sleep Counsellor]. Transcripts of the key presentations are available from Prisca Middlemiss at *Unique* at prisca@rarechromo.org.

Professor Peter Hammond

Nicola Lathey

Emma Hyde

Karen Sutherland

Dr Eugen Strehle

Pattie Everitt