

TYPICAL QUESTIONS AND CONCERNS, ABOUT NIEMANN-PICK DISEASE, RAISED BY RELATIVES AND PARTNERS OF AFFECTED FAMILIES

ABOUT THE DISEASE

What is Niemann-Pick Disease.(N-P)?

"Niemann-Pick" is actually a term for a group of diseases which affect the body's chemical make up and which are caused by specific genetic faults. They are known as lysosomal storage disorders and are inherited as autosomal recessive diseases.

(See the fictitious family tree, on page 4)

What is the history of the disease?

In 1914, Albert Niemann, a German paediatrician, described a young child with enlarged liver and spleen. The child had brain and nervous system impairment and died in less than six months before the age of two. Later in 1927 Ludwig Pick studied tissues, after death, of such infants and provided evidence of a new disease – Niemann-Pick. In 1961 Crocker categorised N-P into types A-D and in 1980 types A and B were shown to be distinct from Types C and D. In 1991 the acid sphingomyelinase (ASM) gene for Types A and B was identified and then in 1997 the gene for Type C.

Is the disease hereditary?

Yes, see the attached fictitious family tree. Both parents, Paul and Carol are carriers. We all carry two genes for all our features whether that be blue eyes or in this case, a disease. When eggs and sperm are made we only put one of these into the egg or sperm. In the case of this family, if John is a carrier, some sperm will have the healthy gene and others the N-P gene and it is pure chance which will fertilise the egg.

Can it skip generations?

Not exactly, but if you look at the family tree for John and Joan, they may have had children that were either OK or carriers, so it would appear that N-P was not in that generation. However, in future generations, if John passed on the gene for N-P to Ian and he met another carrier, Kate, then one of their children would stand a 25% chance of inheriting the disease, in this case, Beth.

So, the disease has re-appeared.

How many people in the UK are affected by it?

Type A is a very acute infantile form of the disease and we have no patients in the UK that we are aware of. In December 2005 we have 17 known type B patients and between 65 and 70, known type C patients.

Is it found throughout the world?

Yes it is, with cases being reported in North America, South America, Europe, Africa, Asia and Australia

Is it more prevalent in male or female?

No, all forms of N-P are autosomal recessive disorders and as such they affect both males and females equally.

Can relatives be identified as high / low risk?

It depends whether they have been identified as carriers.

When one parent is a carrier, there is,

- 2 in 4 chance that the child will be a carrier
- 2 in 4 chance that the child will not have the disease and will not be a carrier

When both parents are carriers, there is,

- 1 in 4 chance that the child will have the disease
- 2 in 4 chance that the child will be a carrier
- 1 in 4 chance that the child will not be a carrier and will not have the disease.

There is a greater chance that the disease will be found in families with a large number of children whilst there is less of a chance that it will occur in every generation. However, because the gene is inherited in a random pattern, families with only two children have been known to have had one child with the disease.

How many different types of N-P are there?

Types A and B are now considered to be one disease, but with different symptoms, caused by the same enzyme defect. Type A being at the severe end of the disease spectrum and Type B at the milder end. Type C is a more complex disease with varying signs and symptoms and with a different biochemical and genetic cause. Types D and E have been mentioned in text books but these are variants of type C.

What are the differences?

Types A and B are caused by a deficiency of an enzyme called Acid sphingomyelinase (ASM) and can be diagnosed by a blood test. Type C, whilst similar in name, is very different and results in excessive amounts of cholesterol building up in the liver and spleen and other lipids building up in the brain. Type C causes a secondary reduction in ASM activity, which is why it is considered to be part of the same disease. Type C is diagnosed using tests carried out on a skin biopsy.

Type D arises in people with a common ancestral background in Nova Scotia and type E appears at the onset of adulthood.

What are the symptoms of the diseases?

Type A is a severe disease with symptoms in the first few months of life, which include feeding problems, failure to thrive, a very large abdomen and progressive loss of all skills. Life expectancy rarely exceeds 5 years.

Type B rarely has neurological implications. Growth may be slow and puberty delayed but patients usually survive into adulthood. A large abdomen caused by a big spleen is common in childhood and respiratory and cardiac problems can occur in adults.

Type C is very variable with some children having a severe form similar to Type A. The disease is neurologically degenerative, often showing itself as clumsiness and a lack of co-ordination. The disease progresses with a slow loss of speech and other nervous system skills, leading to gradual failure of physical and mental function. Type C can show itself at any age and progress over many years or even decades.

Can it occur at any stage in life?

Type A is diagnosed in early life, during infancy. Type B can be diagnosed in childhood if the symptoms of an enlarged spleen are seen, but the symptoms may show much later.

Type C can show itself at any age.

Is it more likely in younger / older people?

Type A is always diagnosed during infancy.

Type B is usually diagnosed in early childhood but can be diagnosed during pre-teen years.

Most cases of Type C are diagnosed in childhood but an ever increasing number of cases are diagnosed in early adulthood. Very rarely, a few cases may be diagnosed in middle age.

TREATMENT

If identified at an early stage, is there any treatment, can it be controlled?

There is no treatment that will cure any of the diseases but therapy and symptomatic treatment can help with symptoms eg. Anticonvulsants for seizures, analgesia for pain.

Can treatment reduce the chances of the disease developing, can it lie dormant, what triggers it?

At the moment, we can do nothing to stop any of the diseases developing. We have no idea why some people start with symptoms very early in life whilst others may reach adulthood before starting with early neurological problems.

Are there cases of full or partial recovery?

No, but in Types B and C the disease may plateau with no obvious worsening of the disease for what can be years.

CARRIER ISSUES

What are the symptoms or consequences of being a carrier?

Carriers themselves do not have the disease, and being a carrier does not affect the mother or father physically, mentally or in any other way. The one consequence of being the carrier of recessive gene is the possibility of passing that particular gene to a child.

What tests are available to determine if a family member is a carrier of the N-P gene?

Once a child or adult is diagnosed, it is possible to look at the DNA to identify the two mutations (abnormal genes) that have been inherited. Once the mutations have been identified, carrier testing is possible and can be discussed with relatives.

However, identifying the two mutations particularly, in type C, can prove difficult. Sometimes, it may only take a short time but cases have been known to take months or even years. In the worst cases, only one of the genes has been identified after many years.

What is involved in being tested for the N-P gene?

Once the mutations have been identified, only a single blood test is needed from each concerned member of the family.

What are the probabilities of me being a carrier if one or both of my parents were carriers?

If you look at the family tree of John and Joan, John is a carrier and Joan is not. If you are a child of theirs, there will be a two in four chance (50%) that you will be a carrier.

If you are the child of Paul and Carol who are both carriers, There will be a two in four chance (50%) that your parents passed on the abnormal gene so you would be a carrier like Katy. There is a one in four chance (50%) that neither abnormal gene was passed on to you. Finally, although you are not affected, there is a one in four chance that a child of theirs will have the N-P disease.

Could the baby of a couple inherit the disease if only one person in a relationship is a carrier of N-P?

No, If only one parent is a carrier, there is, normally, no chance of producing a baby with the disease.

How would a baby be affected if only one parent in the relationship had the N-P gene, could the baby inherit the disease or would the baby be a carrier?

The baby would not have the disease but would have a 50:50 chance of being a carrier

Can babies in the womb be tested for N-P?

Yes, in most cases this can be done by DNA checking or biochemical means. Pre-natal testing for types A and B are accurate and reliable. However, because the primary molecular defect is unknown for type C, it is more difficult to do a pre-natal diagnosis.

If I was a carrier of the N-P gene, can my partner be tested for abnormalities in his genes or clues that may indicate a possible risk of him being a carrier?

At the moment this is not possible, mainly because of the very large numbers of mutations that have already been detected in affected patients.

How many people could be carriers? What statistics are available to allow us to understand the chances of a partner's family having NP and therefore ourselves having a baby with N-P?

If the incidence of NPC is 1:150,000 the chance of anyone in the general population being a carrier is about 1:400.

If you are definitely a carrier the chance of you having an affected child would be 1:800 for each pregnancy.

SCIENTIFIC

If there is known to be type C within the family, would it always be type C that is passed down to the next generation or could it change forms and show as a type A or B?

In this example, it will always be Type C that is passed down

because the N-P Type C gene is on a different chromosome to the Type A and Type B gene.

Is there just one or a number of abnormal genes that cause N-P?

There are over 150 mutations (abnormalities) of the gene that causes N-P Type C. There are also many faults on the Type A and Type B gene that can all cause the disease

Is N-P contagious in any way eg. by blood transfusions?

No, it is an inherited disease.

Is any work being done to develop tests for the partners of people affected by the NP gene?

Not at the moment, but there is a lot of research, world wide on the Niemann-Pick Disease which may help in the future.

What research is being done to find a cure?

Basic and applied research and clinical research has been carried out over the last ten years to understand more about the disease and to find a cure. The work has been carried out by Research Institutions, Universities and Pharmaceutical Companies across the world.

In Types A and B there is a lot of research into medications and enzyme replacement therapies that might slow down the progression of the disease.

In Type C, a lot of research is trying to work out exactly what the Niemann-Pick protein does in the cell which will hopefully point scientists in the direction of medication and cures.

Are there any other diseases related to N-P?

Niemann-Pick disease belong to the group called lysosomal storage disorders among which are several similar diseases. eg. Tay-Sachs Disease and Gaucher Disease. Research into these allied groups may also help N-P Disease.

COMMUNICATION

Why is it so important for myself to be tested, as an adult brother or sister of an N-P carrier, when my children do not have the disease?

It is your choice whether or not to be tested. In your case whether you are a carrier or not, has had no effect on your children. However, there may be a benefit in knowing whether the defective gene has been inherited by yourself and therefore the risk of it being passed on to future generations. These are the sort of issues that can be discussed with genetic counsellors

Should distant relatives be informed that there is N-P within the family , Would they want to know and how should they be informed?

This depends on the family and how well you know them. It is unlikely that they would be affected by N-P but some relatives do like to know. A genetic counsellor is the best person to talk to any extended family.

Does every relative have to be informed?

It is your decision but it is unlikely to affect them unless there are close inter-marital links.

People in the medical profession that we have spoken to, don't know about N-P and haven't been able to talk to us about the risk of having a baby with N-P. Is anything being done to make professional people more aware of the disease?

We are producing as much information as possible in the form of broadsheets and information sheets. These are made available to all professionals involved with families. We also have web sites and awareness weeks.

If the risks of having a N-P baby are small, and future partners of my children cannot be tested, is it worth the emotional trauma of finding out that I am a carrier when I can do nothing about it?

A lot of people decide not to have the test for these reasons but the decision has to be balanced against not knowing the risks to future generations.

If I have had children who do not have N-P, and they are concerned for their future, isn't it more important for them to make their own decision about carrier testing?

As with most carrier testing, these are very personal issues. In a family with normal adult children, this is very often a way round the parents not being tested.

Most genetic counsellors and professionals involved in genetic testing do not provide carrier testing for children unless there is a specific reason for doing so. ie. to prevent problems in childhood as a result of a disease being inherited from a single defective gene. However, when the adult children of N-P carriers or suspected carriers start forming relationships for themselves, they may request a test so as to understand the risks to future generations for themselves and therefore be in a position to make informed choices about their decisions..

Could children who have N-P disease be wrongly diagnosed?

Because the symptoms of type C are so variable, diagnosis is difficult and it is possible that there have been instances where it has been incorrectly diagnosed. Some common errors are;

Attention Deficit Disorder, Learning Disability, Retardation and Delayed Development.

However, beware, N-P is a rare genetic disease, and children in the general population who display these symptoms, will, most certainly, not have the disease.

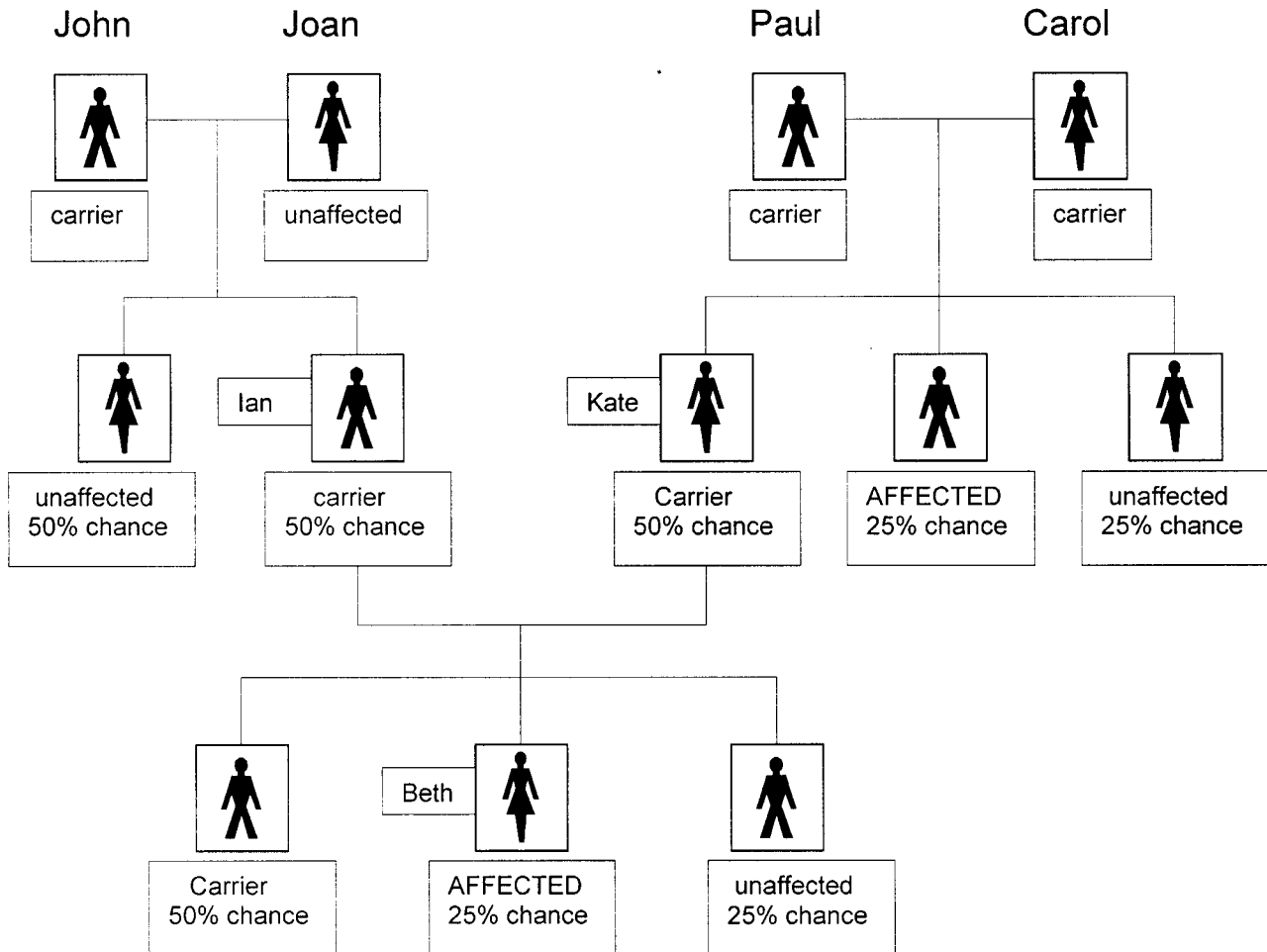
Where do we get information from, if we want to understand more about N-P?

Jackie.imrie@cmmc.nhs.uk or 0161 9222414

www.niemannpick.org.uk or 0191 4150693

Niemann-pick@zetnet.co.uk

A FICTITIOUS FAMILY TREE SHOWING HOW RECESSIVE GENES ARE PASSED ON



When one parent is a carrier, as in John and Joan, there is,

- 2 in 4 (50%) chance that the child will be a carrier
- 2 in 4 (50%) chance that the child will not have the disease and will not be a carrier

When both parents are carriers, as in Paul and Carol, there is,

- 1 in 4 (25%) chance that the child will have the disease
- 2 in 4 (50%) chance that the child will be a carrier
- 1 in 4 (25%) chance that the child will not be a carrier and will not have the disease.

QUESTIONS AND ANSWERS – FEEDBACK

1. Are the questions and answers clear?
2. Can you see any mistakes?
3. Do you have any other questions that we could include?
4. Do you agree to the following methods of circulation? If not, why not?

Newsletter Direct mailing Information pack

Any more comments?

With many thanks to all the families involved