Atherosclerosis: Families at Risk

Uptodate

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Black-and-white
Duration: 00:29:41:09

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<Opening titles>

<Opening film of commuters walking along crowded London streets, including men wearing bowler hats, interspersed with scenes of traffic. Brief close-up scenes in sequence of: exhaust fumes; mouth smoking cigarette; sausages, egg and bacon frying in pan; callipers measuring thickness of skin fat; blood pressure gauge; rotating molecular diagram.>

<Lloyd to camera>

In this programme we're going to consider two aspects of risk of atherosclerosis in families. First of all, Joan Slack will review the relative contributions of the genetic and environmental causes and then I shall talk a little about screening for familial hypercholesterolaemia in children and treatment.

<Lloyd and Slack seated at table with display board for diagrams set between them>

<Lloyd>

So, can I start, Joan, by asking you, is there an increased risk of coronary disease in families of coronary patients?

<Slack to camera>

Yes, there is an increased risk. I think for a long time it's been known that the risk to the relatives of patients who have coronary thrombosis has been increased by about 2 or 3 times that of the general population. Recently, we've done a slightly more detailed study and investigated the risks using life table methods and making allowances for the age at death of the relatives and the increasing risk in successive years. And we have found that for the younger patients, the risk to their younger relatives is rather more than the risk to the relatives of the older patients.

<Slack narrates over slide>

<Slide>

Male Patients

male relatives x5

female relatives x3

Female Patients

male relatives x6

female relatives x7

I think that we can see here that the risks to the younger relatives of the younger patients is 5 times that of the general population, while the risk to the younger female relatives of the male patients is 3 times that of the general population. For the relatives of the female patients, the risks to their male relatives is 6 times that of the general population and the risks to their female relatives is 7 times that of the general population.

<Slack to camera>

I should emphasise that these risks only apply to the relatives of the male patients under 55 years of age and to the younger relatives of the female patients under 65 years of age. It's impossible from these studies to tell whether the increased risk to relatives is due to the common family environment in these families or to their genetic background. And in order to determine how far the genetic background is contributing to the increased risk, we have to turn to twin studies.

In 1970, the results of a Danish twin study were reported and this gives us, I think, quite a good idea of the contribution of the […]

<Slack narrates over chart>

[…] genetic background to the increased risk to relatives. In this study they report the difference between the concordance rate found amongst male monozygotic twins and dizygotic twins, and the female monozygotic twins and dizygotic twins. Where the male of the twin pair has a coronary thrombosis, the co-twin in monozygotic pairs is affected more often than the co-twin in dizygotic pairs. And where the female patient has the coronary thrombosis, the female co-twin is affected really very much more than the female co-twin in the dizygotic pairs. And this is good evidence that genetic factors are playing a part in determining the family risks of coronary thrombosis. There is a little more evidence from the Danish twin study when you look at the co-twins of dizygotic pairs of unlike sex. Amongst the pairs of twins where the male patient is the index patient, only 7 out of 53 co-twins are affected, but where the female patient is the index patient then a really substantially higher proportion of male twins of the unlike sex pairs are affected. And this suggests that the genetic factors are playing a little more important part amongst the females who have coronary heart disease than amongst the males.

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<Slack briefly to camera, then refers to a diagram and draws on it>

Now, how can this be explained? Falkner has provided a model which helps to explain the inheritance of total liability to a common disorder. Total liability is distributed normally in the general population about a mean which I've marked M. For coronary heart disease, there is a threshold beyond which all are affected, and we know that 2½ % of men at the age of 55 will develop coronary heart disease in the following 10 years. These can therefore be marked in fairly accurately. For first degree relatives, the genetic likeness is a half and therefore similarity between the men with coronary heart disease and their first degree relatives will be distributed about a mean which is halfway between that of the patients and the normal population. And this can be marked in by distribution like this. And now I think you can see that quite a substantial proportion of the first degree relatives of affected men have appeared beyond the threshold and can be expected to develop a coronary heart disease before the age of 55.

For women the disorder is very much less frequent and their threshold is further out along the population liability and their first degree relatives will have a liability to coronary heart disease which is a little further out even than the relatives of the men, and their distribution can be marked in in this way. So the relatives of the female patients who develop coronary heart disease have even greater liability to early coronary death than those of the male relatives.

When we use our studies to try and work out how strong is the inherited liability, there is a fairly definite precise definition of inheritability which can be applied.

<Slack narrates briefly over slide and then to camera>

Heritability is the proportion of the total variation which is determined by genetic factors and this can be done by looking at the experience of families of patients with coronary heart disease such as we saw in our family studies. And in that series, for the first degree relatives of male patients the heritability was 60 %, and for the first degree relatives of the younger female patients the heritability was 70 %. This is surprisingly high heritability and doesn't take account of the fact that there may be common family environment playing a part in these families.

We have to think what part the common family environment is playing in families, what part environmental factors are playing and what part inherited factors are playing.

<Slack refers to a series of charts and slides and narrates over them, interspersed with talk to camera>

And I have here put out a spectrum of disorders which we know are mainly due to environmental factors, and we could count smoking amongst the environmental factors which contribute to coronary heart disease, to lack of exercise and to obesity which are beginning to form part perhaps of the common family environment. Obesity we know has some inherited characteristics and we know a good deal about the inheritance of blood pressure measurements and lipid levels as risk factors for coronary heart disease.

00:09:11:13

<*To camera*> Let us consider the effect of lipid levels as a risk factor for coronary heart disease and see what contribution that is making to the risks of coronary heart disease in a population. In this country there have been very few prospective studies, none completed and very few started. But from the Framingham Study we have some very good ideas about the contribution of various risk factors to coronary heart disease and they have been pooled with several other prospective studies and reported by Stamler in his report on the National Pooling Project.

<Next diagram> This shows the distribution of cholesterol level in the American population reported by the National Pooling Project. And the increase in serum cholesterol is shown along the horizontal axis and the coronary mortality rate is shown for each section of serum cholesterol level along the vertical axis. For it's pretty clear from this that there is no increased risk of coronary mortality for men about the mean of the cholesterol, which is at 225, and that the mean coronary mortality rate of this population was about 3.3 % over the following 10 years. The

highest risk is experienced at the upper end of the distribution for cholesterol. And for all men with a cholesterol over 300 milligrams percent, the coronary mortality rate was 5.8 %. This applies to 8 % of the male population. Just to put you into perspective: the same study investigated increasing risks with increasing diastolic blood pressure and found that at the upper end of the distribution for diastolic blood pressure greater than 105 millimetres of mercury, which applied to 6½ % of the population, the risk of coronary mortality in the same age group was 8.9 %, which might be represented up here.

Again, we should perhaps think that half the population are women and their risk is so small that no prospective studies have seriously calculated their risk with increasing cholesterol levels and, in fact, there is no evidence for increasing risks of cholesterol and death from coronary heart disease in the female population. But, there is a very small number of people who have especially high risk of coronary death and these are people with the dominantly inherited condition known as familial hypercholesterolaemia. They form a very small proportion of this population; probably 1 in 250 people in the whole population have familial hypercholesterolaemia. And in the distribution of cholesterol in the general population, only I in 12 people who have cholesterol over 300 milligrams percent will have this raised cholesterol due to familial hypercholesterolaemia. This is a very small proportion of the population, but for people with familial hypercholesterolaemia their risk of coronary death before 55 years of age is not 5.8 % but 50 %, quite out of proportion and off the scale of this diagram.

<*To camera*> This is a very high gene frequency and if you compare it with the other known frequencies of genes in the population, we can look at the known frequency for cystic fibrosis which is 1 in 1,600 <*next slide*> of the population; and for phenylketonuria, another recessive disorder for which we know the gene frequency, this is 1 in 20,000 of the population, and for this disorder, of course, there is screening of every newborn baby in the population.

00:14:09:03

<Lloyd and Slack seated at table>

<Slack>

June, if the heterozygote frequency for familial hypercholesterolaemia is 1 in 250 and we know that the risk of coronary death is so high, do you think we should be screening the population for familial hypercholesterolaemia?

<Lloyd to camera>

Well, if we regard this, first of all, as you've said on a population basis then let's take the newborn population first because it is obviously very attractive to feel that you can collect core blood serum and do a serum cholesterol estimation on it. Unfortunately, this has been done now on a number of occasions and it's quite clear that one cannot screen for this disorder by estimation of cholesterol at birth. If we move up the age span a little into childhood or, indeed, into adult life, we again face a problem in definition because if we go on serum cholesterol values, these, as you've already shown, have a continuous distribution in the population, there is no specific cut-off point at which one can establish the diagnosis and we really can't do population screening on the basis of serum cholesterol for this disease. And until we know the genetic defect and can have a more accurate measure of the basic abnormality, I don't think that population screening is really feasible.

The situation, however, is quite different when comes to families in which the high risk has already been demonstrated. And if we look at an actual example shown in this family tree, […]

<Lloyd narrates over diagram showing family tree>

[…] here we have a family and here are two young children referred to us by the school health clinic because their father died at the age of 27 and he was known to have the heterozygous form of familial hypercholesterolaemia. And both these children, in fact, had inherited the disorder. This then led us to look at the rest of this

family and, in fact, there were already known to be a number of affected adults, some of whom, as you can see, had had coronaries at a young age affecting both men and women. We screened the children in this family and you'll see from the symbols those that were affected. This family tree shows very nicely the dominant mode of inheritance with about 50 % of individuals affected. Now, screening at birth in these individuals is technically possible, particularly if you can do rather more sophisticated methods of investigation which include estimation not simply of serum cholesterol which will not differentiate but of β-lipoprotein cholesterol which will enable you if you know that the parent is a heterozygote to determine whether the child is affected.

<Lloyd to camera>

But when we're screening, we have to remember that we're only screening in order that we can do something for the affected individual and it's a debatable point whether one wants to start treatment in a young newborn baby. My own view here is that we have little evidence that it's necessary to start treatment to lower serum cholesterol at this early age. And I would not advocate a change from breast milk which is known to produce rather higher cholesterol levels in babies to an artificial milk which might lower this if the mother wished to breastfeed. The advantages of breastfeeding are very considerable and would outweigh, I think, any theoretical advantages of changing diet in young babies.

When one comes to the treatment of older children, however, and here I'm thinking of children any age from 1 year upwards, then one can make a good case for lowering serum cholesterol in children with this disorder which as we've seen carries such a high risk of later development of coronary disease. And treatment of children is essentially similar to the treatment that's already been described in these programmes for adults. The two major lines of treatment will be diet, a low saturated fat diet supplemented with polyunsaturated fatty acids, or some form of drug therapy, or possibly a combination. For children we have to be especially careful with drug therapy to avoid the long-term use of drugs which could have unpleasant side effects or, indeed, whose side effects are not yet known. And this really rules out for children dextrothyroxine, nicotinic acid, neomycin and some of the other drugs that have been

described. And we're left at the moment with drug therapy of children relying on a non-absorbable ion exchange resin such as cholestyramine.

00:19:51:19

<Lloyd refers to a chart and narrates over it>

Now, our experience with the treatment of children is shown on this chart here, where we have expressed the degree of reduction of serum cholesterol concentration in children treated either with diet or with cholestyramine, and we use cholestyramine without diet. And we've followed up these children on this slide anyway for three years and I should just emphasise here that we're not looking for a quick immediate effect in these children, we're looking for long-term sustained effect; we hope that this will lowered cholesterol is going to be maintained for many many years. And we see that both diet and cholestyramine lower serum cholesterol concentrations and keep them low. Cholestyramine in this particular study – it was rather more effective than diet.

The other thing that can be seen on this chart relates to these numbers here, which refer to the number of children in the treatment groups. And you'll notice that at the end of 36 months, we have very few children in the 2 groups.

<Lloyd to camera>

The reasons why we have got this reduction in number of children are different for the diet and the cholestyramine treated groups. For the dietary group the reason for the reduced number of children is because, over the course of time, children have got fed up with taking the diet and they've therefore dropped out of treatment. In the cholestyramine treated group, however, we've not been going for so long, this is a relatively new form of treatment in children, and we therefore just haven't followed up such large numbers for such a length of time. I think we can show this problem of compliance with therapy a little better if we look at in life table form.

<Lloyd refers to charts and narrates over them>

And what we have here is the percentage of children remaining satisfactorily controlled on therapy against time of follow-up in years. Let me just define satisfactory control: we've been pretty liberal in our definition, we have regarded a child as showing unsatisfactory control if 2 consecutive serum cholesterol estimations, 1 month apart, have been within 10 % of the pre-treatment cholesterol value. Of course, we would hope that our children satisfactorily controlled would have had a much greater reduction than this.

Now, this is the situation relating to diet and you can see that in a relatively short period of time, a year to a year and a half, the line falls steeply, many children drop out and only about 20 % of the group are still satisfactorily controlled at the end of a 5 year period. Nevertheless, for these children control is good. The reason for this loss of compliance is not that the diet is mysteriously failing in its effect because if we take these children back into hospital or we can tighten up the diet at home, we get a good response. The reason is that in the real life world of these children it's just very difficult to stay on a low saturated fat diet, year in year out, live with your friends, go on holiday etc.

<*Next chart*> Now let's look at the similar sort of life table relating to cholestyramine, the same kind of plan. And here we see that the rate of falloff of compliance is very much slower, that at the end of about 2 years we still have a very large proportion of the group on therapy – it falls off a bit thereafter, but after 3 or 4 years some 60 % of the group are satisfactorily controlled. However, this sounds good but it does mean that 40 % are not satisfactorily controlled and this is not very good when we consider that 5 years out of a life time is still a fairly short period.

<Lloyd to camera>

Now, when we come to consider the reasons for this lack of compliance with cholestyramine, we find that as for diet it's not that cholestyramine is mysteriously losing its effect, it's just that it's difficult stuff to take and we have illustrated as some

of the problems that children and their parents face when taking cholestyramine in this small piece of tape which we recorded before this programme.

00:25:10:15

<Film shows Lloyd seated at table beside a young girl. Drinks are displayed on the table>

<Lloyd>

What are you going to have it in today? Orange, ginger beer, Pepsi, water?

<Girl>

Pepsi.

<Lloyd>

Pepsi, OK. I'll pour the Pepsi, you open the Questran, two packets. That's the dose, isn't it? That's right. You start opening and… *<Lloyd unscrews bottle-top and pours Pepsi into glass>*

<Girl, whispers>

I can't get it open…

<Lloyd>

How are you getting on?

<Girl opens packet of Questran and sprinkles it into glass containing Pepsi>

<Lloyd>

Okay that's good. Sprinkle it on.

<Girl>

Urgh! A big hump.

<Lloyd>

Try not to spill it on the outside. That's fine. If you open the other packet. There it is.

<Girl struggles to open packet>

<Lloyd>

You can do it with your teeth if you want to.

<Girl cuts packet open with scissors>

<Lloyd>

That's right. Now we'll do this a bit more gently. Sprinkle it on. That's right. That's it. *<Lloyd stirs mixture with spoon>* Got it all out?

<Girl>

Not yet, well.

<Lloyd>

Is that finished, both packets empty? You don't want to waste any, do you?

<Shot of Lloyd's hand still stirring mixture to dissolve Questran>

<Lloyd>

Right, how quick's it going to go down today?

<Girl>

<*Laughs*>I don't know. Mmm, it smells funny. <*Takes a sip*> Urgh, powdery. Urgh.

<Lloyd>

Come on, have another sip.

<Girl>

<*Hesitant, then drinks some more*> Urgh. Horrible.

<Lloyd>

Not as good as with water.

<Girl>

Just as bad.

<Lloyd>

Just as bad. Well, it's got to go down, hasn't it?

<*Girl sighs*>

<End of film clip>

<Lloyd to camera>

Well, that was obviously a staged affair and I'm sure that many children and their parents would do a lot better but, nevertheless, this does illustrate the very real difficulties faced in long-term treatment with this drug and I think it's a tribute to many families that they are so compliant and do manage so well. Perhaps the most important thing that doctors can do in helping with management is to realise the difficulties, to support the families and above all to make certain that they maintain contact to see them frequently.

Now, in conclusion I'd like to make four main points. First of all, we've shown that risks of coronary heart disease do run in families. Secondly, we believe that we should be looking at families of coronary patients in order to identify these risks. Thirdly, we should pay special attention to the children in such families because treatment at this early stage may give the best chance of preventing atherosclerosis. And finally, but very importantly, when we do identify one risk factor such as familial hypercholesterolaemia, we should not forget that other risk factors may be present in the same family. We should look for these and if present we should treat them also.

<End credits>