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SUMMARY

Dr. Eamonn Sheridan
Leeds Institute of Molecular
Medicine

Cerebral palsy is the commonest cause of severe physical disability in children in Western countries. It is not a disease but a complex of symptoms and disabilities.

Our project aims to identify the distinct genetic causes of cerebral palsy by studying twenty-two families (with their consent) in the Bradford area with multiple cases of cerebral palsy. The families are all of Pakistani origin and the vast majority of the cases of cerebral palsy are the product of first cousin unions. This particular familial structure gives our research team an opportunity to study recessive disorders, which arise as a consequence of a single gene being handed on down both sides of the family from a single carrier ancestor.

If we can identify distinct genetic causes of cerebral palsy, this will have a major impact on our understanding of this common disorder. It will provide evidence for biological causes of cerebral palsy, which we hope will enable us to medically intervene to treat and prevent its progression.

Wellbeing of Women spoke to Dr. Eamonn Sheridan to find out more about his project on 'Uncovering the genetic causes of Cerebral Palsy'.

What made you want to become a clinician?

When I was fifteen I had an acute bowel perforation and was in hospital for three weeks. At the time it seemed that I was really ill, but I realise now that I made a very rapid recovery. Up to then I had no interest in medicine at all and in fact I did Latin O Level in preference to Biology! My experience in a pretty small hospital converted me to the idea of being a doctor and after that I was hooked. The combination of being so obviously involved with helping people and being asked searching questions was pretty irresistible.

What attracted you to this particular area of research?

Cerebral palsy is one of the commonest causes of disability in the developed world. When I was an obstetric junior doctor the major cause of cerebral palsy was regarded as birth accidents. However over the past twenty years there has been a shift in perception. We now realise that cerebral palsy is the end result of a cascade of influences, many of them related to events before birth.

It was already clear that genetic influences probably played a role. However the major drawback to studying the role of genes in common diseases is that it requires the collection of huge datasets involving hundreds if not thousands of patients.

Collecting a data set of a couple of thousand patients with cerebral palsy would be a major challenge. However I observed several families in my clinical practice in which there were siblings and even cousins with cerebral palsy. These children were born at term, with normal birth weights and appeared fine as babies. There was nothing to suggest that they would subsequently develop cerebral palsy. The structure of these families, where marriage between first cousins is common, made it highly likely that the cerebral palsy had a genetic basis, and that it was in fact being inherited as a simple autosomal recessive condition. The recessive nature of

the condition meant that we could take a short cut to genetic analysis. We were able to identify shared genetic factors between children with cerebral palsy. These genetic factors were not found in their siblings who did not have cerebral palsy. We were then able to rapidly find the faulty gene and to identify mutations in the faulty gene believed to cause cerebral palsy. To date we have identified mutations in three different genes in separate families.

How did you feel when you were awarded your project grant from Wellbeing of Women?

I was delighted to receive the grant, this allowed us to appoint a highly skilled scientist to the project and to analyse lots of families we had previously contacted who were keen to get involved in our research.

The prevailing view is that cerebral palsy is caused by oxygen deprivation during birth, what led you to believe that genetic factors may be involved?

There is a lot of epidemiological data which indicates that oxygen deprivation is not the only cause. Very careful studies of the pattern of cerebral palsy in families from Sweden, Australia and North America indicated that genetic factors in the babies were very likely to be involved. We also had data on the incidence of the disorder locally in Yorkshire which confirmed these findings and suggested that there was an autosomal recessive component in at least some families.

Were the Asian families in Bradford keen to take part in your study?

The families were keen to be involved. The disorder had almost always come as a complete shock in a child who was previously well with no obvious risk factors. The risk of recurrence in families was not one that had been addressed so those families with more than one affected child were particularly keen to follow up a genetic cause. We were helped by the fact that we already had Urdu and Punjabi speaking research nurses in the department who could interview patients, provide them with information about the

study and answer questions. It would have been very difficult to recruit patients without the help of those nurses.

The Muslim community is usually keen to help with research, the precepts of Islam encourage this. We were able to engage with individual Asian families, very few declined to take part.

If we can identify genetic causes, what steps can we take to intervene to prevent cerebral palsy?

The identification of the biological pathways which lead to cerebral palsy will hopefully lead to the development of new drugs or other treatments which can ameliorate the effects which result in cerebral palsy. One of the genes we have identified had already been the subject of investigation for targeting with new drugs by the pharmaceutical industry. None of these are available yet for clinical use, but this indicates the possibilities.

Cerebral palsy is sadly a leading cause of disability in children, is there any treatment available at the moment for children born with the condition?

At present there is only limited

treatment to deal with the results of cerebral palsy. Children are offered physiotherapy, Occupational Therapy and appropriate aids to daily living, but there is no curative treatment at present. For the children who suffer brain damage at birth and who are at high risk of cerebral palsy, treatments such as cooling - which are in clinical trial at present - are currently being developed.

Will your research aim to reverse the effects of cerebral palsy on children or act more as preventative measure?

It is unlikely that we can reverse the established brain injury that results in cerebral palsy, our hope would be to prevent the disorder in those at risk.

Has the project thrown up any further and/or unexpected avenues for research on this subject?

Not as yet.

Where can you see your research and career heading in the next 5-10 years?

The needs of the local community are such that it is unlikely we will have identified the genetic causes of all the conditions that affect them over the course of the next couple of years. It is highly likely we will still be encountering

novel conditions even in ten years. I will probably still be trying to identify new disease genes. However I am increasingly interested in the biology of the new disease-causing proteins we identify so I see myself using more cell biological approaches than straight genetics over the next 10 years or so.

What are your realistic hopes over the next ten years for preventing this complex condition?

I think it is unlikely we will be able to prevent all cases of cerebral palsy. It is a very complex condition and is probably the end result of a variety of different disordered pathways. However, we should be able to improve our ability to identify pregnancies and children at risk of the condition; we will then be able to medically intervene to ameliorate the problems. This is why it is so important to discover the underlying causes; it is only through dealing with the underlying causes that we can hope to prevent cerebral palsy.

We are very grateful to 100 Women in Hedgefunds for their support of Dr. Sheridan's Research in 2008 through the Stanley Fink Memorial Fund Project.

Wellbeing of Women study explains link between Smoking and Ectopic Pregnancies.

Wellbeing of Women funded scientists have recently revealed a major discovery as to why women who smoke have a higher risk of developing ectopic pregnancies.

Facts:

Around one in 50 pregnancies in the western world is ectopic. The condition is the leading cause of maternal mortality in the first three months of pregnancy.

There are more than 30,000 ectopic pregnancies in the UK each year, with the egg implanting in the Fallopian tube in 98 per cent of cases. This can cause the tube to rupture and lead to internal bleeding and fertility problems in the future.

Smoking is thought to increase the risk of an ectopic pregnancy by up to four times.

Researchers found that female smokers who have had an ectopic pregnancy have raised levels of a protein- called PROKR1 – in their Fallopian tubes, which increases the risk of an egg implanting outside the womb. The project looked at tissue samples from female smokers and non-smokers, and from women who had previously had ectopic and healthy pregnancies were both analysed.

The project was based at the University of Edinburgh where the team there believe that a chemical in cigarette smoke – called cotinine – triggers a chain reaction that increases PROKR1 in the Fallopian tubes. While this protein allows the pregnancies to implant correctly inside the womb, its presence in the Fallopian tubes is believed to increase the risks of implantation outside the womb.

The work, published in the American Journal of Pathology in November, found that women who smoked and had developed an ectopic pregnancy had doubled the levels of this protein in their Fallopian tubes compared to women who did not smoke and had previously had a healthy pregnancy.

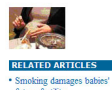
Researchers also believe that too much PROKR1 prevents the muscles in the walls of the Fallopian tubes from contracting, which in turn hinders the transfer of the egg to the womb.

Right: The project received great publicity in a number of publications, these are a few examples.



Smoking linked to ectopic pregnancy

Smokers increase their risks of having an ectopic pregnancy by up to four times, according to research. The University of Edinburgh study, which was funded by the Wellbeing of Women charity, linked smoking to a protein that is thought to increase the chances of an ectopic pregnancy. Ectocysis is a condition that affects up to 30,000 women in Britain every year, and is caused by a fertilised egg being implanted outside the womb - usually in the fallopian tubes.



Smoking link to ectopic pregnancy

A chemical in cigarette smoke has been found to cause a reaction which can lead to ectopic pregnancies, according to Edinburgh scientists. Research from experts at Edinburgh University said Cotinine triggered a reaction which increased a protein in the Fallopian tubes. They said the protein, called PROKR1, raised the risk of an egg implanting outside the womb. Smoking is thought to increase the risk of an ectopic pregnancy by up to four times.



Dr Andrew Horne of the University's Centre for Reproductive Biology who led the study said:

“ This research provides scientific evidence so that we can understand why women who smoke are more at risk of ectopic pregnancies and how smoking impacts on reproductive health. While it may be easy to understand why inhalation of smoke affects the lungs, this shows that components of cigarette smoke also enter the blood stream and affect seemingly unconnected parts of the body like the reproductive tract. ”

President of the Royal College of Obstetricians and Gynaecologists - Tony Falconer, discusses Research and Training

How important do you think it is to fund new research into obstetrics and gynaecology?

I think if you look back in the developments certainly in my life time, in terms of obstetrics and gynaecology, they are all on the back of research. If you think back to the time of the war when the main killer of women was sepsis, the introduction of antibiotics was an innovation that really completely transformed healthcare. More recently products like Anti D have stopped rhesus iso-immunisation and some forms of chemotherapy have translated into better outcomes for cancer care. There is a whole spectrum of opportunities that have arisen as a result of research and these should continue. The conflict in the current situation is the amount of money available in the financial recession we are in - the amount available for research is very limited. This is a major major worry. If you look at the potential genetic advances in the next few years I predict (I may be wrong) in 10 years time you will be able to have a simple blood test and probably through a computer system be able to dial up what is going to happen to you in your lifetime. You may not want that information but that is the kind of sophistication we are getting to.

If you look again at the challenges in obstetrics and gynaecology they are still huge. The real and biggest problem that we have in obstetric practice is premature labour. The outcome for babies even when they are born at 28 weeks today - they may survive, but their outcome is probably not as good as those babies that go to term. It is a major major challenge to understand why premature labour arises, how we can stop it and how we can prevent it. If you look at gynaecology we are making huge advances in terms of the medicalisation of various conditions, so that we don't always have to do operations anymore. There is a huge area for improvement in my own area of cancer care. In my lifetime the outcome for cancer of the ovary has not changed and that is going over 35-40 years of clinical practice. So whatever area you look at, there are huge opportunities for research and the spectrum of obstetrics and gynaecology is so wide that those research areas encompass almost every area of our discipline.

What would you say to encourage a young medical student thinking of becoming an obstetrician or gynaecologist?

This is a very fascinating question and one that we address ourselves because not long ago we had a major recruitment crisis within our discipline but I think of all the disciplines that there are, obstetrics and gynaecology covers such a wide area.

If you are a surgical type of person then you can go into cancer care or urogynaecology.

If you are interested in childbirth, the rewards are obviously huge and I always say that if anybody doesn't get a kick out of delivering a baby then there is something slightly unusual about that person. It is one of the most thrilling things and great privileges to be involved with.

If you are interested in epidemiology - the study of information and information systems - then again there are major areas where you can make a contribution.

If your bend is more psychiatric or psychological again there are huge areas that you can get involved with.

So I think although most disciplines offer a breadth, the breadth that you can get in obstetrics and gynaecology is very considerable. However there are certain qualities which you need to have to be an effective obstetrician and gynaecologist and the discipline is not appropriate for somebody who has major problems with making acute decisions. The labour ward in particular, where you tend to start your training, requires you to make decisions quickly and if you cannot do that you are in serious difficulty and it will cause you major agitation. There are plenty of other disciplines where you can be more introspective and thoughtful but obstetrics does lend itself to rapid decision making. So I would encourage anybody to become an obstetrician and gynaecologist -and I don't know many people who I meet that have



President of The Royal College of Obstetricians and Gynaecologists - Tony Falconer

been unhappy with the decisions they have made. It's also a great passport to the under-resourced world because the conditions of care in many of those countries are appalling and the challenges particularly for maternity care are really quite phenomenal. Again especially for young people who have significant altruism, this will satisfy those needs for those doctors.

If there were no Wellbeing of Women Research Training Grants, how do you think this would affect research or indeed practice in obstetrics and gynaecology?

Well I think any funding agency makes a major contribution in terms of the opportunities for doing research. If you look at Wellbeing of Women in particular, by giving opportunities for young trainees to be involved in research, this often opens a door that will lead on to a lifetime in very major research. Now I think everyone will accept that sometimes applied clinical research is not quite as complex as the sophistication of some very complex basic scientific research. This is where I applaud Wellbeing of Women because they offer opportunities for young doctors who previously wouldn't have had that chance and they can obtain some very meaningful data from those results, which go on to help the healthcare of women. A very classic example of this is in terms of cervical screening methodologies, some of the initial work was sponsored by Wellbeing. Also if you look at urogynaecology (a common problem of stress incontinence for women) which is a very debilitating condition) but is not life threatening, again a lot of the good work in that has been supported by Wellbeing of Women. So I think if there wasn't that opportunity then some of our young doctors would never get a chance or flavour of doing research and for many people that can stay with them forever.

There are other opportunities but they are highly competitive and very restricted. The opportunities for research today are not what they used to be and sadly it is no longer considered a vital part of your training and portfolio to go through a period of academic work. You could argue also that that may be an advantage because only the people who are very motivated go into that area, and there is some truth in that. So I think Wellbeing of Women provides a very important vehicle and opportunity or people to have a flavour of research that will alter the way they practice clinical medicine, and may alter the very way that they unfold in terms of their own clinical trading and contribution.

Is there currently a shortfall or are we in danger of a shortfall of young doctors entering this speciality?

I am pleased to report that in terms of obstetrics and gynaecology that we had a very major problem a number of years ago, which seems to have been turned round because I think people realise obstetrics and gynaecology is a very attractive discipline. The things that frightened people away were hours of work but that is now controlled by a European legislation and also I think one cannot deny that the magnitude of responsibility of a middle grade trainee running a busy labour ward is phenomenal and that degree of responsibility is not for everyone. Litigation is very common particularly in obstetrics and again that was perceived to be something that frightened people away. But with the increasing number of graduates from our own medical schools, we are now in a very healthy position and I'm pleased to report that virtually every training opportunity in the United Kingdom is now being taken up by graduates from the United Kingdom. We have been in a situation for a number of years where a large number of overseas graduates have come and filled these opportunities. Now this is a very good thing if they are going to take their skills back to their motherland but what happened was many of these doctors actually settled in the UK, so they haven't been able to transport those skills back to their homeland.

In the current economic climate, do you think that this kind of funding will increase in importance?

I think inevitably the recession and the dip in the financial opportunities must mean that we are more and more reliant on organisations like Wellbeing of Women. I think there is no doubt if you look at what is happening with the university structures at the moment, they are under very real threat with the fee structure going up and all the other variables. I think Wellbeing and other organisations are absolutely vital and I applaud their attempts to increase revenue, so that projects and young researchers can be helped.

Why does the RCOG work in partnership with Wellbeing of Women?

Well our discipline represents the educational and standards aspirations for women's health, so we're concerned with improving women's healthcare everywhere in the world, wherever they are. So any organisation that is concerned with raising the standard of healthcare through research or enquiry we would support. Our relationship with Wellbeing of Women is rather different because we are joined at the hip - we are not completely one organisation but it is nonetheless a very intimate relationship. People from our side (from the Royal College) are involved in the committee structure of Wellbeing of Women and indeed in terms of determining where the dispersal of monies will go with the particular projects. Wellbeing of Women, particularly the lay people who are fantastic in terms of generating enthusiasm and fundraising, look to us for leadership in terms of dispersal of funds and I think that is a very healthy and an entirely appropriate way to work as a collaborative if you like.

“I think Wellbeing and other organisations are absolutely vital and I applaud their attempts to increase revenue, so that projects and young researchers can be helped.”

President of The Royal College of Obstetricians & Gynaecologists - Dr. Tony Falconer

We would like to thank all of our supporters who enable Wellbeing of Women to continue investing in medical research of the highest quality to improve the health –and in many cases to save the lives of - women and their babies.

We are very grateful to the following charitable Trusts and Foundations who have made major contributions to our research in 2010 into gynaecological cancers and into life-threatening complications of pregnancy and birth: The Herbert & Peter Blgrave Charitable Trust; The Eveson Charitable Trust; The Grimmitt Trust; The Caron Keating Foundation; The Dowager Countess Eleanor Peel Trust; The Connie & Albert Taylor Trust; The Rothermere Foundation; Sir Samuel Scott of Yews Trust; The James Tudor Foundation and The Welton Foundation.

Wellbeing of Women and The Royal College of Obstetricians & Gynaecologists

We are the official charity partner of The RCOG, we work in partnership to improve women's health.

We rely on their expertise to provide top quality health information and help us choose the best research.