

MND Matters: Episode 5: Let's Talk Research

Intro: You're listening to MND Matters, a podcast from the MND Association.

Nick: Welcome to MND Matters, brought to you by the MND Association, alongside members of the MND community, including people affected by the disease, health and social care professionals, and supporters, we will be bringing stories, information and expertise direct to your ears. Subscribe to ensure you don't miss an episode. I'm Nick and I work in the research team at the MND Association.

Becky: And I'm Becky. I'm one of the Area Support Coordinators down in Sussex.

Nick: Those of you who would have heard some of our previous podcasts will notice we have a new co-host with us today and it is my pleasure to introduce you to Becky.

Becky: Thanks Nick. Thanks for having me. In this episode 'Let's talk research' we'll be touching on just a few aspects of MND research. We're going to be exploring topics and questions frequently asked by the MND community and discussing some of the research behind it. For more information about any of the topics raised in this episode please do take a look at our website and also check out the research blog. Also, just to say, later on we'll be hearing from Dani Baird who's living with MND, and she's currently taking part in a clinical trial, and we're going to hear from Professor Martin Turner who's a Neurologist and researcher on the genetics of MND.

Nick: And it's my great pleasure to introduce Dr Brian Dickie, the Director of Research and Development at the MND Association. Brian's been working at the Association for over 20 years. Brian, nice of you to join us today.

Brian: Thanks for the invitation Nick.

Becky: And, also Nick, you're here wearing two hats this week because you're not only the host of the podcast but you're also Head of Research so looking forward to this episode. So, one of the main questions that I think I hear a lot from our MND community is do we have a lab in the office Brian?

Brian: There's a quick answer to that which is no we don't. We're a research funder and I guess a research facilitator as well. So, if I explain a little bit about the funding first of all. We, at the moment, are funding over 80 grants and that's a collective commitment of over £14million – that's spread over several years. We also fund mainly in the UK but will fund anywhere in the world, you know, if it's going to give us the answers to the questions. It doesn't matter whether it's in London, England or London, Ontario if it's the highest quality research and the greatest relevance to MND.

We do have a couple of criteria though. One is that the work needs to be unique in concept or design. In other words, nobody in the UK is already doing that sort of research and the second one is there has to be a kind of formal collaboration with a UK research team or a research institute and that way we make sure that new knowledge, new skills, new expertise are drawn into the UK to help to build up our own research base. So, you know, we expect the researchers to collaborate and we also try and collaborate as a funder as well with other funding agencies.

Becky: So it really is like a global effort isn't it? It's really interesting to know that you collaborate and I suppose it would be interesting to know how you choose what research to fund.

Brian: Yeah, that can be a challenge because opportunity exceeds resource, greatly exceeds resource. We can only afford to fund about 1 in 5 of all the ideas that come in through the door so we have a process to separate the wheat from the chaff. It's called peer review. Many organisations

use this. We send each application out to leading experts around the world and then we have advisory panels who come together twice a year to go through every single proposal and determine which ones are of the highest quality and greatest relevance to MND.

And all of that fits within a broader research strategy. So, I mentioned the 80 projects earlier. They all fall within 4 key themes.

The first is what we call identifying targets. So that's understanding the causes of MND, developing better models of MND in the lab so, in other words, something in the lab that actually mimics what's going on in the patient and homing in on the pivotal processes that determine life or death for the motor neurone. A great example of collaboration is the international Project MinE programme which is the world's biggest gene hunting programme on a single disease and we were involved very early in that study. It now involves 20 countries around the world, all trying to understand the genetic basis of this disease.

You know, once you've identified these targets, and that's what drug companies want. They want something to shoot at, so they need to know what these pivotal processes are. You can move on to saying okay, how can we turn that into treatments and that's a whole programme of drug discovery, drug development, all the way through to clinical trials. Recently, we announced a joint funding call with a charity called LifeArc which is kind of a leading UK charity when it comes to drug discovery and drug development and we're hoping to turn this one-off call actually into a more productive long term initiative because we can learn so much from them. And they actually have a good track record of taking ideas from the lab, pooling them through into clinical trials and then, of course, getting them on the market and that's what we're looking for as treatments.

So, the third area is really understanding the human disease and that means that you need to really study what's called phenotyping. Understanding how the disease progresses physically, on the outside, but also what's happening on the inside as well so we fund a lot of what's called biomarker research and that involves taking blood samples, CSF samples, saliva, urine as well and analysing for chemical changes that are happening within the body as the disease manifests and as it progresses.

And then finally, the fourth area is I'd call it the care because there's an awful lot we can do while we're waiting for these drugs to come through the pipeline into clinical trials and we really need to understand how best to provide timely, coordinated multi-disciplinary care. And that's not just having an impact on quality of life, it's actually having an impact on quantity of life as well. And it links back to clinical drug trials as well, because we need to make sure that all the hospitals that are participating in trials are providing that same high quality standard of care so that we're not throwing additional noise into clinical studies.

Nick: I think it's important as well Brian to say that not only do we fund projects but we also fund people and we have different types of grants for that which is really great and we're trying to underpin really the best and brightest people and keep them in MND research.

You also touched on the kind of international effort looking at motor neurone disease and, you know, we organise the Symposium. You must have seen that change considerably over the years you've been working for the Association.

Brian: Yeah. I mean it certainly changed recently as you and I know when we've gone online. The first Symposium, which pre-dates me I have to say, attracted about 40 delegates and was held in Solihull, the Swallow Hotel in Solihull in Birmingham and it's changed a lot since then. Now, we have usually at least 1200 delegates turn up to the face to face event and, as we discovered last year

when because of the pandemic we had to move online, we actually increased our reach and we had over 1800 delegates from a record 48 countries around the world. And that collaboration, that cross-fertilisation of new ideas, new discoveries, from all the different sub-fields of MND research is so vital because in a rare disease in particular like MND we can't have people operating in silos. We've got to have this international collaboration that transcends individual institutes or indeed national boundaries.

Nick: I think that question of collaboration is really key as well in cracking these big questions. I think there's a great example of that recently which is the Covid vaccination. You know, people would say to us often 'how come there is a vaccine for Covid but there's no cure for MND?' I mean, I think we know the answers to that but do you want to just touch on that for us Brian please?

Brian: Well, certainly, I mean you know the first thing is Covid is a single cause disease. It's caused by a virus whereas MND is much, much more complex than that. If you consider that the strategy for Covid is actually a 200 year old tried and tested approach which is vaccination - that's been around since the days of Edward Jenner and Louis Pasteur, albeit, the current Covid vaccinations have a 21st century twist to them.

But, that said, there's a huge amount of learning we can take from the Covid experience. First of all, this unprecedented collaboration and sharing of new data and new information between academics, between governments, even between drug companies. Now, you know, they don't normally do this so I think it's encouraging for the future that, hopefully, we'll see less of a silo mentality there. I think the other thing is it's amazing how you can cut through the bureaucracy when you really need to. You know, we've seen trials that have been set up within a few weeks whereas this would have usually taken months, sometimes even years. I think we need to take this forward, this sense of proportionality, into other life-threatening diseases. But, of course, I think the main challenge is what they also brought to the Covid battle was money, a lot of money. You know, it's certainly not a panacea for everything but certainly multi-billion pound cash injections certainly help.

You know, I am increasingly encouraged that we're seeing more investment in MND research, particularly from drug companies because they're starting to address neurodegeneration because there's such a big unmet need there. I think one of the encouraging things is that they're coming into neurodegeneration but a lot of them are starting to say, well actually we think, although MND is a smaller market, it's a rarer disease, we actually think it may be more tractable than Alzheimers and Parkinsons so therefore maybe we'll focus on MND first. And then if we can crack that, it will open up these bigger markets.

You know, I think there's a lot of excitement at the moment that we can take the explosion of new knowledge that's happened over the past 20 years and start to move away from asking the question 'what's going on here?' to 'well, we're starting to understand what's going on here, now what can we do about it?'. You just need to look at a condition called spinal muscular atrophy which is a childhood motor neurone condition and we now have effective treatments on the market for that. Now, spinal muscular atrophy is not adult onset motor neurone disease. The vast majority of cases occur in the first 6 months of life and motor neurones in a 6 month old or a 2 year old child are very different from the motor neurones in a 50 or 60 year old person. But it's proof of principle. It shows that motor neurones can be protected and so we are now taking these strategies forward to see if they work in some of the inherited forms of the disease initially and, certainly, we don't have all the read outs from the trials yet because they're still in progress but the initial findings are certainly very positive.

Nick: And those companies that have created really those therapies for spinal muscular atrophy are also the same companies that are backing these treatments and trials in motor neurone disease so that is really a new dawn, a new era that we're getting into with potentially gene therapies. You mentioned inherited MND. I mean that's one of the questions that we often hear is 'if someone in the family has MND, does it mean that I will get it too?'. We know there are some genes associated with MND and we posed this question actually to Professor Martin Turner from the University of Oxford.

Dr Martin Turner: The short answer to the question is no because the majority of MND cases arise from a complex mixture of factors in which a person's genetic make-up is just one aspect. All of us are a mixture of our parents' genetics and we're put together in a different mix from any siblings that we have. And our own children are similarly a mixture of our own DNA and that of their other parent and there are actually very few medical conditions that are inherited in a totally predictable way. And single cases of MND in a family are simply usually a one-off and we call that sporadic with no significantly increased risk to close relatives. Now in about 10-15% of people with MND, we can identify a change in the code of a single gene that has definitely driven the development of the condition largely on its own. And many of these individuals will have a positive family history whereby one of their parents or a sibling also had MND or sometimes they had a rare type of dementia called FTD, which can be another manifestation of one particular genetic change. And these rarer single gene changes that cause MND do carry a 50/50 chance of being passed on to each of the children that that individual might have. But, even so, this doesn't always mean that that child goes on to develop MND during their natural lifetime, even if they are a carrier of that gene change.

Now, a difficulty can arise when a person doesn't know their family history, perhaps because they were adopted or their parents died at a young age, potentially before MND had a chance to show and so remained hidden in that generation. But in those circumstances, it's still most likely that someone with MND is an isolated case and that it won't be inherited in a simple way. Now genetic testing can be requested by anyone with MND but it shouldn't be done without understanding what it can and what it can't show and it's definitely something to discuss very carefully with a neurologist who specialises in MND.

Nick: I think that gives us a real understanding that obviously MND is a complex disease with, as we mentioned before, there are many potential different causes that have to combine together for somebody to develop the symptoms.

Brian: Yes. I think another important thing to mention is that although we've found many of the genes involved in MND, especially in the inherited forms of the disease we've found about three-quarters of the genes, of course that means that there's still a quarter that we haven't found and so a negative gene test won't inform us about that. So, you know, even if someone takes a genetic test, you can't rule out genes that you haven't yet discovered.

I think a real driver for more genetic testing, particularly in the diagnostic process, is going to be the emergence of effective treatments that target these genes, these antisense treatments that are being developed at the moment.

Becky: It's really fascinating listening to you both talking about this but as a non-medical person or researcher or scientist, there's often questions that we hear from what we see in the press and at the minute we're seeing lots of exposure from the amazing Doddie Weir and Rob Burrow so you can't help but think the question of 'is there a link between sport and MND?'. I just wanted to throw that to you but in a simpler way.

Brian: Well, there isn't a simple answer I think is the first thing. Certainly, it does appear that people who are diagnosed with MND tend to have a history of being fit, sporty, athletic. Martin Turner who we just heard from often says that if somebody comes to my clinic looking for diagnosis, I often look at the thickness of their medical folder and if it's very thin, in other words they haven't got a history of lots of other illnesses, that actually can be an indicator that it might be MND. So, particularly the link with sport, it's a tricky one because the way these links are established is through a process called epidemiology. It's often looking at large numbers of people and looking at their lifestyles, their diets etc and it can be a very blunt instrument. It's very good at generating associations, links but it doesn't actually establish definitively whether something is a cause or not. Now we know that MND is what's called a multifactorial disease and there are a number of events have to occur, a number of steps that have to occur in order to tilt the balance in favour of the disease occurring. I often use the analogy of a set of balancing scales, like the Scales of Justice, and something has to tilt that balance and many of these factors are like grains of sand on one side of the scales. No one on their own causes the disease. It's the combination of genetic grains of sand, of environmental grains of sand that build up over decades perhaps, and it might be the timing as well – exactly when it happens is so important. So, it's really difficult to unpick what these grains of sand are.

You know, for example, going back to sport, there's been a suggestion that maybe concussion or trauma can be a predisposing factor in MND. But there are other factors that have to be brought in as well. For example, sportsmen of course exercise a lot, that's the nature of their business. So, if you are exercising excessively, are you actually kind of wearing out your motor neurones faster? There's some evidence that that might be the case but, once again, it's very, very subtle and probably isn't sufficient on its own and certainly, of course, the health benefits of exercise far outweigh any small increased risk of developing MND.

But there's another theory as well. So, this is where I can kind of try and differentiate between association and causation and that is, okay, let's say we find more sportspeople are likely to develop MND and we say, well, it must be something to do with that sport, that occupation. Well, it could be completely unrelated. There's a lot of evidence that people with MND exhibit what's called a cellular hypermetabolism. In other words, their cells are burning energy at a slightly faster rate than the rest of us and that's effectively something they're born with and, therefore, if you are hypermetabolic as a child then maybe you're a bit more active as a child and therefore you get drawn into sport at an early age as an outlet for that activity and you stick within that sport and you're more likely to become adept at that sport to the extent that you play it professionally. And so the fact that maybe more professional sportsmen appear to have MND is not linked to their sport or the exercise or the head injuries. It's actually linked to something that is going on in their cells and has been going on since before they were even born.

So, we don't have any clear answers here. We have hints about what's going on and certainly, of course, we need to explore these further to try and really get to grips because there is the possibility that we could actually start to give advice to younger family members, particularly where the scales are loaded by a particular genetic predisposition. There could be kind of dietary, lifestyle advice that might just help to ensure that the scales don't get loaded too quickly.

Nick: We know 6 people are diagnosed with MND every day in the UK and 6 people die and there is a lifetime risk of 1 in 300 but all those people are not sportsmen or women and so is this anecdotal? What are we doing to kind of find out what people have done in their past life histories, careers, that kind of thing and exposures?

Brian: Well, one of the things we can do first of all is establish a national MND register so that we're identifying every single person in the country because there are some even more fundamental

questions than the one you've just asked. We don't actually know how many people there are with MND in the country, so if we can establish a national register that ideally picks up close on 100% of everybody who's diagnosed with the disease, we'll know how many there are, we'll know where they are so we can start to see if there is any aspect linked to their particular geography, their local environment, what sub-types of MND are they and in what proportions, what care is available.

And then the next layer down is, if you are in contact with everybody, is you can start to do some more detailed epidemiology studies and asking people about their lifestyles, their diets. You know sometimes this can be fraught with difficulty because these events may have happened 30, 40 years ago so asking a person what they had for breakfast 30 years ago may not be the most accurate. So, it's not going to give us all the answers but certainly the first bit is actually having a population based register that's picking everybody up because, that way, when you're asking the questions to people, then you know that you're asking it to everybody and not just a select sub group of people which might actually skew the results.

Becky: Is MND more likely to affect men than women?

Brian: Yes. Overall, it seems to be a ratio of about 3:2 male to female, however, it gets closer to 1:1 with age. So, certainly post-menopausal, it's much closer to 1:1 and, you know, that raises theories in itself. For example, the effect of oestrogens in the body and there is some evidence that oestrogens might actually help to protect neurones to a certain extent and that's a line of therapy development that has been looked at. I have to say it probably hasn't really delivered yet.

Becky: That just goes to show how important it is about the MND register and building this better picture and understanding across the country.

Brian: Yeah, and, you know, in future we'd like to see the register as actually being the gateway to taking part in other sorts of research, you know clinical research, even clinical trials.

Becky: Brilliant. So that leads actually quite nicely onto another question we hear daily I think in terms of how can you take part in MND research or what does that look like, because there's lots of different types of research isn't there?

Brian: Yeah. It can look very different depending on what you are doing. You know, taking part in research can be as simple as taking part in the national register, giving a blood sample for genetic analysis, taking part in healthcare surveys and then, of course, it can also mean taking part in clinical drug trials as well. I think probably the most interest is in the drug trials and I have to stress first of all that drug trials are medical experiments. They're not treatments. They are absolutely vital to first of all work out if a drug's working or not but also to establish whether it might not be working and, you know, one of the frustrating things over the past 25 years is that more trials have actually had to be stopped because of the side effects than have actually made it through to marketable, effective treatments. And, you know, that's one of the reasons that we're also very cautious with any recommendation for unapproved and untested treatments because they do have to go through this rigorous evaluation process.

So, the encouraging thing is that there are more trials coming down the pipeline. As I mentioned earlier, there's an unprecedented number of drug companies interested in this area. We have new trial platforms that are, hopefully, going to make the process much more efficient, much less expensive and much faster and, you know, that means smaller, cheaper, smarter and indeed more trials. So, the MND-SMART platform which is being rolled out across the UK and the TRICALS

platform which is a pan-European initiative bringing together the leading centres in many European countries are going to be absolutely fundamental to this in the future.

Becky: Brilliant. We're actually really fortunate enough to have spoken to somebody called Dani Baird who is living with MND and she has agreed to tell us a little bit more about the research that she's taking part in. Dani was diagnosed back in 2014 and she's actually the fifth person in her family, the fifth of her siblings to have been diagnosed with MND and the research trial she is taking part in is absolutely fascinating and links with what you were saying before about the genetics. And she's just got a wonderful way of explaining her situation and it's a very positive message so this is what she had to say when we caught up with her earlier.

Dani: I got involved with the SOD-1 trial in Sheffield soon after I was diagnosed simply really because of my Professor at King's College, Chris Shaw. I just went all out to find something. You know, I just knew I wanted to find something. I know we're only a small proportion of MND sufferers, 2% I think, but it was really important for me to find, or do, something to help. Help me as well as help the cause and it's worked for me so I've been very lucky. I didn't have any fears. I'm quite a relaxed kind of person and the lumbar punctures I suppose a lot of people would be scared of but I'm quite sort of tough like that so, no, I wasn't at all scared. They were so nice. Everybody is so nice treating me so I've never felt scared, never.

I go into the Research Centre in Sheffield which is attached to SITraN and I have loads of, they monitor me totally because Biogen requests that. So, I have blood tests, I have breathing tests, I have those things where you do your heart and, you know, everything, muscle testing, and at the end of it I get a lumbar puncture in which they go into my spine, they take fluid off and then they put the drug in. But I'm so used to it now, it doesn't bother me at all and they've learned to do it very well. I've had several different doctors do it but they're all so good and I have a fabulous nurse who looks after me so it's all fine. Somehow, being stuck at home with MND it was quite a change and I quite liked getting out there and meeting people and having a purpose and having a reason to go somewhere. And I go to King's Cross and I sit in the First Class lounge and it's all paid for by Biogen and then I go First Class up to Sheffield and the rail staff are just amazing. No, I've never found it a burden. In fact, secretly, deep down I quite look forward to it because I know all the people in the Research Centre now and they know me and it's like old friends so it's nice to go back and see everybody so, no, it's never a burden.

The thought of being able to help. I've got children and the future and it's time something was done about this awful disease. It's horrific. I'm the fifth one in my family to have it and we've lost 4 members, brothers and sisters, so I'm sort of, there's a big reason for me doing this which makes it all worthwhile.

Becky: Wow. That's a really positive message there from Dani but I suppose it's worth mentioning here about clinical trials and the way they work and do we know that it's working and I guess understanding in a layman's term what happens when somebody goes on a clinical trial and then the information we get out at the end of it. Nick, I don't know if you've got any reflections on that particular clip there from Dani.

Nick: Yeah. That's a really positive story. We must caveat that with we don't really know if the trial is working yet as it's still ongoing but Dani certainly feels that it's had a significant influence on her MND progression. You know, it's amazing to see the commitment really and the partnership that people living with and affected by MND are prepared to go to to take part in these trials. You know, that's something that we're so privileged to have such a great community that's willing to take part in these things because it is a significant amount of effort and commitment.

Brian: The trial that Dani is participating in is what we call targeted therapy so it's not going to be available for everybody with MND. The chances are it will only be effective in a small proportion of people with this particular inherited form of the disease, but I think what it illustrates is that we can't treat MND as one amorphous disease. We have to treat it as many diseases that have similar symptoms and therefore therapies will be more personalised, more bespoke to each particular form of the disease. But I think it's really exciting. I think if we can make inroads, even in just one sub-type of the disease, it's going to open the door to many, many more opportunities for treatment.

Nick: That's really where we want to be. More people in trials. You know, MND isn't incurable. We think it's underfunded and, as Brian said throughout this podcast, you know there are more and more trials taking part and more companies interested so the time really is now. There's real positivity in the air and I think, you know, we keep driving MND research forward and we'll get to that place we want to be – a world free from MND.

Brian, on that note, you know, I feel quite optimistic with great hope for the future. You've been in your position for quite some time and, you know, how do you feel now? Do you think that we really are pushing at the door for effective therapies and treatments and something is around the corner? How are you with your optimistic view or otherwise?

Brian: I certainly think we're closer than ever before. I often use a rather clichéd expression that we might not quite see the light at the end of the tunnel yet but the train is heading in the right direction and it's picking up speed. I think we just need to look at other diseases to see how things can change. Multiple sclerosis is one. Cancer is another and in fact I think we should have the ambition to maybe be a little bit more like the cancer field where they have that ambition to get every person diagnosed an opportunity to take part in a therapeutic study and also, as a kind of consequence of that, research becomes an integral part of the care they receive and I think that is quite profound because you don't treat care and research as two different things. They're all part of that holistic approach to treatment.

Becky: It's a really positive message and I feel like it's been a really positive experience to be able to ask these questions to you both on behalf of the MND community because I know that these are things that people living with MND or affected by MND sit and think about quite a lot. Probably, quite a lot of hours have been dedicated to the questions and answers that we've put to you today so I just wanted to say thank you for taking the time to explain it. And, what you just said there about people taking part in clinical and research as part of, alongside the care, I know that our MND community fully believe in that. I've never met a group of people that have been more driven to find the cause and the cure than people living with and affected by MND so it's just wonderful to be able to have the opportunity to have this access to you guys and share that on this podcast and I just wanted to thank you.

Nick: Thank you so much. I want to say a great big thank you to Brian for taking part in this podcast and thank you Becky, co-host, and also thank you Martin Turner and Dani for taking part as well and answering some of our questions. If people have particular topics they'd like us to discuss in some of the future podcasts as well, please get in touch with the Association and let us know and we'll be more than happy to consider that and, hopefully, there'll be many more podcasts like this on research in the pipeline.

If you've been affected by anything you've heard in this podcast, please head to our website or contact MND Connect, our helpline, where we'll be more than willing to answer any of your questions and signpost you to other resources if required.

Thank you for listening. Bye for now.

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