



The Path to a Cure Interview with pediatric MS specialist Brenda Banwell

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Multiple sclerosis is usually thought of as a disease that strikes in adulthood. But in reality, MS can also affect people at a very young age – even children who are just a few years old. Childhood MS presents many challenges for families and healthcare providers alike, especially since medical practices and resources for people with MS have been mostly oriented towards adults. However, childhood MS also provides many opportunities not available in adult MS to understand how genetic and environmental factors interact to cause the disease.

Dr. Brenda Banwell of The Hospital for Sick Children in Toronto (also called “Sick Kids”) is one of a new group of pioneers exploring the world of pediatric MS. She is working both to improve the care that children with MS receive and to better understand how MS develops in children through clinical and basic research. Together with colleagues Doug Arnold, Amit Bar-Or, and Dessa Sadovnick, she recently launched a five-year study called, “Demyelination of the Central Nervous System in Canadian Children.” This innovative project aims to enroll, follow, and study 300 children with an initial demyelinating symptom to identify factors that may predict or trigger their conversion to definite MS. To learn more about this study and other aspects of her work at Sick Kids, Boston Cure Project’s Hollie Schmidt recently talked with Brenda about the issues and opportunities presented by pediatric MS.

Can you tell us about how you came to work in the field of pediatric MS?

A few years ago, when I was doing my fellowship at the Mayo Clinic and preparing to come back to Sick Kids, I received a phone call from someone at the Toronto chapter of the MS Society of Canada. This person told me that five families had registered with them who had children with MS and who felt a little bit lost. I was asked whether I would look after them. All five children were under the care of neurologists, but were not receiving care in a focused MS clinic. Two of the children had been seen in an adult MS clinic, but had found this very intimidating. An 8-year old doesn’t belong in an adult hospital or an adult waiting room, particularly in an adult MS clinic where some of the people there may be quite far along in their disease. I said I’d be happy to help these families.

Once I was back at Sick Kids I discussed the situation with my nursing staff, Jennifer Boyd and Lynn McMillan. We realized that we were being asked to care for children for whom there were really no existing services – there were no clinics focused on childhood MS at that point and very little ongoing research focused on childhood MS. There certainly were some groups around the world who had done some nice work in the area, but there wasn’t a big childhood MS presence and to the best of my knowledge, childhood MS had never been presented at the major meetings or conferences as a course or seminar. We decided that if we were going to start a pediatric MS clinic, we had to start it properly, with a multidisciplinary approach in which people could work together to understand the complexity of the disease. We

arranged to have occupational physiotherapy, psychiatry, and neuroophthalmology, and eventually a clinical coordinator (funded by the MS Society). We started the clinic in October 1999 and it has grown and grown, following not only children with confirmed MS but also children with a first attack of demyelination who are at risk for MS. All told we look after over 200 children now, of whom 50 have confirmed MS.

What types of clinical research and related programs have you launched there?

One of our biggest concerns is the effect of MS in childhood on learning, cognition, and academic performance. We've done one research project in that area and we're in the process of designing a grant to look at this in more depth across the ages, from our youngest to our oldest children. My nurses are also just now completing a quality-of-life project looking at how children cope with the diagnosis of this disease, how they feel, what their questions and needs are, and how we should address them, because there's not a lot on that either. In terms of clinical education, we work with the National MS Society in the US and the Canadian MS Society who have been putting together a series of programs and informational materials for children and families with MS. That initiative started just two years ago in collaboration with Lauren Krupp in the US and other people around the world.

We're also working on educating our colleagues because there are still plenty of professionals out there who don't think that MS can happen in children. For instance, a lot of doctors seeing a child who has optic neuritis at age 7 and hemisensory loss at age 9 just wouldn't think about MS in this scenario. This delays diagnosis for the affected child, who continues to complain about things like fatigue and slowing down academically in school, but nobody recognizes that it's part of a disease process. So we've spoken on this topic at several meetings. There is now a pediatric MS program at the American Academy of Neurology that Lauren Krupp, Anita Belman, and I chair. I also chair a symposium on childhood MS at the Consortium of MS Centers, and we're starting to work towards something similar at the European MS conference. We've worked really hard at trying to disseminate information about childhood MS in multiple places because there are many more children who have this disease than are recognized.

Along those lines, do you think that growing awareness of MS in children is responsible for what seems like an increasing number of pediatric MS cases being identified? Or could it actually be that more kids are getting MS now than before?

Well, that's a hard question, because if something was poorly diagnosed and underrecognized before, then it's hard to know whether or not we just missed it. My sense is that it was there all along and we missed it, because if you query adults with MS about when they think their disease started, about 25% will tell you that they knew something was wrong at least in adolescence, if not before. This is not the best methodology of course, because it's retrospective, it relies on memory, and it's biased entirely by the fact that the people asked know they have the disease now. But even if that number is an overestimate, it still suggests that the number we currently use, which is that 3-5% of all MS patients start in childhood, is a gross underestimate. Probably somewhere in the middle is the true percentage of MS patients for whom the disease, at least clinically, started in childhood. And now it seems we're starting to identify 10 to 15% of MS patients before adulthood, because

of MRI, increased awareness, and education. But this still doesn't tell us whether the total value has truly increased.

What would these kids who have MS but were "missed" have been diagnosed with, if not MS?

One of the most popular terms has been "post-viral something," even when no virus can be identified. A lot of people believe that if someone had a viral infection within 3 months of their demyelinating event, that's significant. Well, if you take a group of Canadian children in January and ask how many of them have had at least sniffles or some sort of a cough, you're going to get 85-90% positivity, because that's what we have in the winter. Nonetheless, viral infection may be a trigger of demyelination, and viral exposures in childhood may be part of the environmental component of MS etiology.

A lot of physicians also use the term ADEM, or acute disseminated encephalomyelitis, to describe any form of demyelination in children. If a child comes in with optic neuritis in one eye and their MRI shows 10 to 15 lesions, but they have no symptoms from those lesions, many pediatricians, and pediatric neurologists for that matter, would say that the child has ADEM. Whereas if that were a 25-year old young woman, we would say she has optic neuritis and is at a high risk of MS. Of those children who have classic ADEM which presents as fever, headache, confusion, seizures and multiple other neurological problems, 30% will go on to develop MS. I'm sure the percentage of children with optic neuritis and 15 MRI lesions would be much greater. I'm part of a working group through the NMSS that will develop a working definition of ADEM to help pediatric healthcare providers in using this term. Also, in our prospective 5-year study of every child in Canada with their first attack of demyelination, we will obviously be looking to see whether an ADEM type of presentation is more likely to lead to MS compared with other presentations.

In addition to misdiagnosis, the lack of desire to make a life-long diagnosis in a child is a reason why children might not be thought about as having MS. Nobody wants to wrongly tell a child that they have MS, and find out later that their immune system settles down and nothing further happens.

The other very real possibility is that certain symptoms may be underreported by young children. A 6-year old may not articulate, "My arm is numb," as well as a 46-year old would. The other one that we probably miss a fair bit is unilateral optic neuritis. When you think about it, even adults often don't notice that one eye is blurry because they very quickly compensate for it.

Does pediatric MS differ in any significant way from adult MS, aside from the earlier age of onset?

One difference seems to be the impact on learning, particularly for the children that present under age 10. They are having inflammation and disease activity occurring prior to completing their core educational building blocks, so those children seem to be the ones who develop more problems with their academics later on. We don't have enough data yet to say this with confidence, but in comparison to an adult MS population, the types of deficits seem to be a bit different. And that's not too

surprising. Someone whose ability to learn basic things such as mathematics or advanced sentence structure is disrupted might have quite different issues compared with an adult who had already acquired all that. Also, the frequency of a multiple symptom onset may be a little bit higher in children than in adults. Kids might have a more dramatic first attack than you might see in adults.

Do you treat it any differently? I understand none of the MS-specific drugs have been tested specifically in children yet, do you use them anyway?

We do.

How do you know how to use them in children?

We're obviously very careful with them, so we start at lower doses proportional to the size of the child, and increase gradually toward the full dose if the child can tolerate it and it's appropriate. We monitor liver function and blood count for the children on interferon very carefully, and that has been just fine. Certainly we see our children more frequently and are more vigilant about side effect profile analysis than you might need to be in an adult population where those side effects are better understood. But truthfully the kids tolerate the medications very well.

I know it's hard to tell because you're not doing a controlled study, but do they seem to respond to the drugs?

They do. You're quite right, the accurate answer to that is it requires several hundred kids and a control population to be certain,. But clinically, the children do seem to have a reduction in their relapses, their MRIs seem to stabilize, and the families and the clinicians here and in other centers that I've spoken with also believe that these patients are doing very well on these drugs. So we all feel confident that we're doing the right thing in treating children with these drugs. Overall, I'd have to say the drugs seem to be working quite nicely, with the obvious limitation that that's not based on a scientific study.

Let's turn now to your five-year study of children with initial demyelinating attacks. What are you hoping to learn about the causes or triggers of MS through this study, and what other topics are you exploring?

My personal biggest interest in MS, which I think this population can address better than any adult population, is the question of what triggers MS. A very young MS population is uniquely able to indicate if there's an environmental trigger, whether it's a positive trigger (something that you acquire), or a negative trigger (something that you should have had but didn't receive). In a 30-year old with MS, there are 30 years worth of environmental triggers, events, exposures, etc. to try to sort through. On the other hand, a 5-year old is much closer to the biological onset of the disease.

We've been focusing on viral exposures, not that we think a particular virus causes MS, but perhaps the sequence or series of viruses you're exposed to in early childhood modifies your immune system in such a manner that it could respond against yourself.

My collaborator Amit Bar-Or works with me on all of my projects, and his focus is on the immune system of MS patients. We feel that if you look at the initial immune target of the MS disease process before the disease has been present for very long, we may be able to identify the initial inciting antigen. That would be very exciting in terms of therapeutics. It may also help in terms of recognition and diagnosis of MS, because if we can tell which antigen is being targeted in someone's first attack, we might theoretically be able to predict who's going to be more likely to develop chronic disease versus who's going to recover.

The other main area of our work is using MRI to diagnose and understand MS in children. In terms of diagnosis, we have already established that the current adult criteria do not apply particularly well to MS in children. One component of the McDonald criteria requires nine T2 lesions, which comes out of the fact that adults often have had other things such as small strokes or hypertension that can cause white matter lesions. Requiring nine lesions helps avoid mistakenly lumping someone with hypertension into the MS population. However, we don't have a whole lot of hypertensive children, so perhaps this criteria should be changed for children. The things that you have to rule out in children are different from the things you rule out in adults, and the MRI appearance of controls not surprisingly is also different, so our criteria are going to be a little different. Working on this is very important, because if healthcare practitioners had an MRI scoring tool that gave them confidence in distinguishing childhood MS from other conditions, it would be of great value to our patients. That is why we are currently developing MRI criteria for children.

In another application of MRI, with Doug Arnold, we're using advanced techniques to look at the non-involved white matter in 3-, 4- or 5-year olds at their first demyelinating attack, to help answer the fundamental question of whether white matter is abnormal in persons with MS from the very start. This question has been addressed in adults before, and we do see abnormalities in the normal-appearing white matter at the time of their first attack in MS, but nobody can say whether those have been there for life or developed later as part of the disease process. However, if the white matter is very abnormal in someone who is 5 or younger at the time of the first attack, we have to question whether it was abnormal from birth. We're also looking at things such as white matter atrophy and white matter maturation. One question we're asking is whether the progressive loss of white matter in children who have had their first attack can confirm or predict that they will go on to develop MS. One would imagine it probably does, but no one's ever studied that. No one has also ever looked at what happens if you disrupt primary maturation of the white matter. Myelination of our brains isn't complete until almost 20 years of age, so if you start demyelinating when you haven't even fully myelinated, what happens? In other words, do children with MS have more deficits down the road in terms of cognition because the primary white matter formation was disrupted in the first place?

In addition to our MRI collaboration, we are working with Dessa Sadovnick and George Ebers on some of their genetic questions. We want to know whether one of the reasons why some people develop MS very early in life is because they have a greater number of genetic risk factors for MS. So we are involved in a pretty broad range of studies.

I'd say so! Perhaps one of the benefits of being in this relatively unexplored territory is that there are so many things you can investigate if you have the right people involved.

You're quite right – there are so many areas that are wide open for review. But it's not that we are scattered, I don't want to give that impression. The Canada-wide study is a very cohesive, coordinated study. We've created databases that are all linked. Although we are doing multiple analyses, we have crafted the data analysis component of our study to allow that to all be pulled in and linked together. Our overall goal is to find out whether we predict MS in the cohort of children who've had their first attack. If we can, what are the predictors? We've kept our minds completely open. It may be a set of clinical symptoms, it may be a particular MRI appearance or recovery pattern, it may be the initial target of the immune system, it might be a genetic link, or it might be a combination of several things. If you believe in MS being a multi-hit disorder where you have to have several things stacked together in the wrong direction to lead to an MS outcome, then perhaps by looking at this cohort of children we can pull them out. So although we have multiple areas of research, we have linked them together in an organized, structured way so that we can interpret them in light of each other.

Presumably you're going to have a lot of data when all the results are in. How are you planning to analyze it?

Well, we have a whole team of statisticians which helps. We're also using some database interfacing which the Center for Computational Biology here at Sick Kids has facilitated.

When do you expect to have something to report from this study?

Well, we just launched in September, so realistically, I think that we will be reporting the most exciting data at least two years from now. We may have some preliminary MRI data to look at within a year, because we do MRIs at baseline, 3 months, 6 months, and 12 months. But the main product of this grant, the result of the predictive model of MS outcome, is five years away because we can't finalize it until we have all of our data.

Another piece of the project that we'll be able to report every year will come through a surveillance program that the Canadian Pediatric Society operates for diseases of interest to child and youth health. Every five years they choose around seven or eight diseases to monitor and have recently included demyelination of the central nervous system. Through this program every pediatric healthcare provider in the country, even if they're not at one of our 22 research sites, will receive a notice every month asking them to report if they've seen any children with demyelination. Anyone who does report will then get a more detailed reporting form which is anonymous and therefore doesn't require informed consent from the family. So over the five years of this program we will have annual incidence data, an annual review of what the presentations were, and where they were located across Canada.

Is Canada the first country to do something like this?

Yes!

Let's look back a little bit at your previous research. At the Boston Cure Project we're primarily concerned with finding out what causes MS, and so we were very interested in the paper you published in JAMA in April that had some noteworthy results concerning the Epstein-Barr virus (EBV). Could you recap these findings for us?

This study related to our question of whether or not particular exposures in the environment, such as viruses, trigger or foster an abnormal immune response that leads to MS. We looked at the Epstein-Barr virus first because it's a very powerful virus in the human immune system. It's also ubiquitous, so in Canada 97-98% of the population ultimately are exposed to it. When we initially proposed to investigate it, a lot of people wondered how EBV can possibly relate to a disease like MS when everybody is infected. Our response is that it may not be a question of whether you get it but when. We hypothesized that if you're exposed to EBV during a particular window of risk, such as a certain age range, it may modify how your immune system responds to future events. What we found is that Canadian children with MS were much more likely to have been exposed to EBV than their age-matched non-MS counterparts. Now if our observation is relevant only in Canada, then you have to ponder what that means. However, if it's relevant across the world despite different geographies and different environments, then our finding has a lot more power. So we've since expanded our investigation to a six-country study of childhood MS, which is taking place in Canada, the US, Argentina, Finland, Italy, and Russia. We presented our preliminary international data at ECTRIMS, and so far it shows the same results we had in the Canadian data, with 80-85% of children with MS being positive for remote EBV infection, versus somewhere between 25 and 40% of controls.

By the way, one of the world experts on EBV is Dr. Ascherio at the Harvard School of Public Health, and he and his group of epidemiologists have been studying EBV in adult MS for a long time.

How might one interpret these results?

Well, they might mean that EBV triggers or is involved in the early events of MS, or they may just mean that children with MS are more prone to EBV. One step we're taking to help answer this question is including a very detailed panel of about twenty viruses in our prospective Canada study, so when children come in with their first attack, we can see whether they've had EBV or other infections. If EBV is there at the first attack, that supports the idea that it's a trigger; if it comes between the first attack and second, it may be a propagating agent.

The next step involves designing some assays to look at how T and B immune cells behave. In other words, although we all get EBV, perhaps our immune systems handle it differently. If you have been infected with EBV, the virus will live in your B cells. It remains dormant, but it's always there. One question is whether there is a difference in the proportion of infected B cells in people who have MS versus people who don't. Another question is, do people who have EBV infectivity have a different immune response? Normally, our T cells monitor the number of EBV-infected B cells in our bodies, and if there are too many, the T cells come along and dampen them down. One thing to ask is if you have MS and you receive your EBV infection when you're young, what happens to your T cells? Obviously they've proliferated to protect you from EBV, but in doing that did something about the EBV viral protein

trigger those T cells to enter the brain and react? We know that there is at least one region of EBV nuclear protein antigen that has a similar genetic sequence to myelin basic protein (MBP), so could this allow T cells to react against MBP because they previously had to react against EBV? And does this happen at a key vulnerable age when something is happening in myelin maturation or otherwise to allow this abnormal reaction? That's a pretty broad question and there will not be a simple answer, but we're designing some assays to see whether children who have MS react differently to certain antigens compared with children who don't, and then we'll try to see whether that plays a role in how the immune system reacts to actual myelin preparations. There's a great deal of work to take what is currently an observation and move it towards a theory and then towards something more concrete, and we are very much at the beginning. But we have some ideas and we're moving forward.

We know that Epstein-Barr persists in our cells and can be reactivated. Do you think this reactivation could also be involved in triggering relapses on an ongoing basis?

That's been postulated as a factor in adult MS. We don't know yet whether that could be important in kids because we're just starting to look at that. It's entirely possible that relapses are not due to the activity of the virus, but rather the reactivation of the immune system. In anyone who's ever had EBV, periodically during the year, EBV reactivates and is released from the body which is why it's so infectious. As that process happens, every time it happens, your immune system has to respond. So your T cells have to increase in number and they have to dampen down this proliferating virus again. If your T cells are more active, one could postulate that that might lead to an increased chance of there being an MS attack. So it may not be that the virus itself is in the brain, but just that it triggers your immune system to activate again, which leads to an increased number of circulating immune cells, some of which go into the brain and cause yet another attack. That's very theoretical, but it might be true.

Is anyone working on EBV vaccines to prevent infection, or treatments to keep it from reactivating, if we should find that EBV is involved in triggering MS and/or relapses?

Yes, and no. The problem with vaccines for EBV is that you would really have to understand our biology better to be sure that's the right thing to do. When you give a vaccine, like the measles-mumps-rubella vaccine, it's usually designed to instigate immunity against the virus by creating a circulating set of immune cells that were stimulated against the vaccine. In other words, you get the immune response without having a real infection. In MS, it may be not the infection that's the problem but the ongoing immune response, in which case a vaccine may not be the way to go. My other comment which is more philosophical is that any virus that has survived to the degree that EBV has, and can exist in almost every person, suggests that somehow it may confer an as-yet unrecognized advantage to humans. Rarely in nature does a virus or other infectious organism survive and become ubiquitous in the environment unless the host either gains an advantage from it or is unable to kill it. So before you would want to modify something like that, you would really want to understand what it does. We know for example that EBV in equatorial Africa leads to Burkitt's lymphoma. You might question then why it hasn't been weeded out in humans there. One of the reasons is believed to be that it has some protective effect against malaria. So we need to understand EBV better before we would want to wipe it out, and we also need to understand whether trying to wipe it out might just

instigate the disease in everybody. If you gave the vaccine to everybody at the same age, and that age happened to be a bad time for their immune system, we could theoretically make the MS problem worse.

Remember that the data we have on EBV is just a highly statistically significant observation. Our responsibility now is to take that observation now and study very carefully its association with the disease to be sure we understand what it means. That's not a simple process, and we're certainly not suggesting that the virus itself causes the disease. We're looking at a very complex interaction between the immune system, the environment, your own genetic predisposition and a little bit of chance. I don't think any one thing is going to be the final answer, but who knows? Cervical cancer is now largely known to be an infectious disease – and nobody predicted that 20 years ago.

Thank you so much for your time today! Before we wrap up, is there anything else you'd like our audience to know?

The one thing I always emphasize is that none of what we do would be possible if the MS societies hadn't been so supportive of our work. In our case, the Canadian MS Society and the MS Scientific Research Foundation have been particularly supportive. They had the confidence to invest in a group of MS patients that people previously didn't even think about. I know that all the families I care for are enormously grateful that these societies have placed an interest in helping children and understanding their disease. One other thing I'd say is that the biggest thing we can do in childhood MS is to work together. We are already part of a national and North American collaboration on this topic, and now we also see an emerging interest in international collaboration which is terrific.

Note: To find out more about the 5-year study on "Demyelination of the Central Nervous System in Canadian Children," funded by the Multiple Sclerosis Scientific Research Foundation, please go to: <http://pedsdemyelination.ccb.sickkids.ca/>