



No Detail Too



Small

*Children and adolescents
receive comprehensive care in
the UB Pediatric MS Center*

STORY BY S. A. UNGER
PHOTOS BY K. C. KRATT

In April 2006, when Olivia Ballard was 14 years old, she mentioned to her mother, Tawnya, that the vision in her right eye was blurry and that she had a headache above the eye.

Tawnya attributed it to Olivia's allergies and her wearing makeup to bed, and casually reminded her daughter to take her medicines and remove her makeup before bedtime.

A week later, when Olivia complained to her mother that her vision was "really blurry" and that she still had the pain, Tawnya made an appointment for her to see an optometrist in their hometown of Delaware, Ohio.

After the optometrist examined Olivia, he asked her to leave the room and told Tawnya that her daughter's optic nerve was swollen. He referred them to an ophthalmologist, who confirmed the diagnosis and called Olivia's pediatrician.

When a magnetic resonance imaging (MRI) scan that the pediatrician ordered revealed lesions on Olivia's brain, he referred her to a nearby children's hospital.

The neurologists at the children's hospital admitted Olivia for three days of intravenous steroid therapy and then sent her home for several weeks of oral steroids. "The doctors there mentioned MS [multiple sclerosis] as a possibility," says Tawnya. "But then they said, 'No, it's not MS; it's just optic neuritis.' So we went on, and everything was fine."

Then, on Christmas Eve of that year, Olivia told her mom that her feet were numb.

While Olivia's case is all-too familiar to the physicians in the UB Pediatric MS Center, cases similar to hers still can result in a delayed diagnosis or a misdiagnosis in other settings since the perception is that "children don't get MS."

“I didn’t think too much about it,” says Tawnya. “She had been sick with a bad cold and had been lying around a lot, so I thought it was a circulation problem—something like that.”

The symptoms persisted and worsened. “It was like my feet had gotten cold,” recalls Olivia, now 17, “and the numbness just never went away, but slowly worked all the way up to my waist.”

Tawnya called their pediatrician, who told her they needed to go back to the children’s hospital.

“I was caught off guard,” says Tawnya. “I said to him, ‘You mean it’s associated with something like that?’

“I didn’t put it together. We had gone from April to December and nothing had happened, so I thought she was fine.”

When Tawnya contacted the children’s hospital, she was told that the neurologist whom Olivia should see was on vacation, so they needed to go

directly to the emergency room instead.

After an eight-hour wait in the ER, Olivia had another MRI that revealed lesions on her spine, so again she was admitted to the hospital for three days of IV steroid therapy.

During this stay, the pediatric neurologists at the hospital diagnosed Olivia with multiple sclerosis and referred her to the Cleveland Clinic. Tawnya called the clinic on January 3 to make an appointment and was told the first available time was February 22.

Grateful for the referral, she scheduled the appointment but, like any parent, she worried about time passing and felt a sense of urgency.

She immediately went online and visited the National Multiple Sclerosis Society website, where she found a description of the Pediatric MS Network, which is made up of six centers of excellence around the United States that specialize in the diagnosis and treatment of pediatric multiple sclerosis. She scrolled through the list of designated sites, hoping to find one nearby.

To her relief, she saw that there was a center in the Women and Children’s Hospital of Buffalo, operated by the Jacobs Neurological Institute, home to UB’s Department of Neurology.

“I called the [Pediatric MS] center and reached Jennifer Ray, the nurse,” recalls Tawnya. “I had Olivia’s MRI report, so I was reading it to her, and she must have spent 45 minutes on the phone with me that first time and answered all my questions.”

Two weeks later, the Ballard family made the five-and-a-half hour drive to Buffalo, where Olivia was examined by Bianca Weinstock-Guttman, MD, director of the Pediatric MS Center of the Jacobs Neurological Institute, University at Buffalo, and Ann Yeh, MD, co-director of the center.

The family stayed in Buffalo for three days for Olivia to be comprehensively evaluated by the center’s staff, which include specialists in multiple sclerosis, pediatric neurology, pediatric neuropsychology, MRI diagnoses, neuro-ophthalmology, urology, and pediatric nursing and rehabilitation, all of whom are supported by a dedicated medical social worker who coordinates all aspects of care and provides what center staff refer to as “single-point accountability.”

While the family was elated to find this level of comprehensive care for Olivia, the visit was sobering.

“We had already been told that Olivia had MS, but when Dr. Weinstock-Guttman and Dr. Yeh examined her and said, ‘Yes, she does have MS; I don’t know, it was a feeling I can’t describe,’ says Tawnya. “I already knew it, but when you hear it officially from people who have been deemed experts, it’s so hard.”

That first year, the Ballards made three more trips to Buffalo; currently, they come twice a year.

Both Olivia and Tawnya say they don’t know what they would do without the support of the staff at the UB Pediatric MS Center.

“Any time I need help with anything, there is somebody I can call; or, if I email, I know I’m going to get an answer back right away,” says Tawnya, who has



ANN YEH, MD, left, AND BIANCA WEINSTOCK-GUTTMAN, MD, CO-DIRECTORS OF THE UB PEDIATRIC MS CENTER

needed ongoing assistance with issues related to side effects of the interferon medications Olivia is taking, as well as difficulties her daughter is having in school due to her MS.

Olivia says she too looks to the staff for help any time. “Last summer I was having a rough time,” Olivia says, “and I called Jennifer [Ray] and talked to her for an hour, and I felt so much better—and I love Dr. Yeh and Dr. Weinstock-Guttman and Mary [Karpinski, the social worker]. They’re the best.”

Marshalling Shared Resources

WHILE OLIVIA’S CASE IS ALL-TOO FAMILIAR to the physicians in the UB Pediatric MS Center, cases similar to hers can still result in a delayed diagnosis or a misdiagnosis in other settings since the perception is that “children don’t get MS.” Although this misperception is changing, children with the disease still run the risk of being labeled “lazy” or “problem children.”

Even when children are correctly diagnosed, they can be stigmatized in this way, feel isolated, do poorly in school and struggle to cope with frustrations the disease can bring if they and their families don’t receive specialized care and support backed by state-of-the-art education and research programs.



OLIVIA BALLARD, right, WITH HER MOTHER, TAWNYA, AND BROTHER BLAKE DURING A RECENT TRIP TO BUFFALO

PHOTO BY BRIAN SMISTER

It was with this type of specialized environment in mind that the National MS Society formed the Pediatric MS Network in 2006, at which time UB's Jacobs Neurological Institute was chosen to be one of the network's six sites and awarded a \$1.8 million grant to establish the center at the Women and Children's Hospital of Buffalo. (The other regional Pediatric MS Centers of Excellence are at the Children's Hospital of Alabama, University of Alabama at Birmingham; Stony Brook University Hospital, Stony Brook, New York; Mayo Clinic, Rochester, Minnesota; Massachusetts General Hospital for Children, Harvard University; and University of California at San Francisco, Regional Pediatric MS Center.)

While the recurrence of these demyelinating events is key to a definitive diagnosis of MS, Weinstock-Guttman explains that she and her colleagues do not wait for this to happen but instead proactively monitor the children with MRI scans, which can highlight the presence of clinically silent lesions.

The grant to the Buffalo center builds on the pioneering work conducted by the late Lawrence Jacobs, MD, a longtime professor and chair of neurology at UB who developed treatments—including the interferon drug Avonex—that helped to redefine the standard of care for adults with MS.

As envisioned by the National MS Society, the six centers of excellence around the country are charged with providing care, educating primary care physicians and families, and collaborating on research studies to maximize data gathered from the population of pediatric MS patients they treat.

Aggressive Diagnosis

MULTIPLE SCLEROSIS IS AN AUTOIMMUNE DISEASE in which a person's immune system attacks myelin, the fatty protective sheath on nerve cells. Because myelin helps conduct nerve impulses that send messages between the brain and body, its loss, or "demyelination," can cause

such symptoms as impaired vision, movement, balance, speech and cognitive ability.

With the advent of new diagnostic tools and techniques, it is now estimated that 8,000 to 10,000 children in the United States currently have MS, and as many as 15,000 may have related symptoms.

For reasons that are not yet clearly understood, Western New York has the second highest rate of MS in the country for adults (160 cases per 100,000, compared to the national average of 50 cases per 100,000). Although physicians hypothesize that children are affected less often than adults, not enough data is available to prove this.

"The usual age of onset for MS is between 20 and 40, but there are cases that are clearly initiated earlier, before age 18, so we know children can have the disease," says Weinstock-Guttman, associate professor of neurology, who also directs the UB Baird Multiple Sclerosis Center in the Jacobs Neurological Institute, where adults with MS receive comprehensive care.

She explains that it's important in the pediatric population to distinguish between MS and other demyelinating disorders, such as acute disseminated encephalomyelitis (ADEM), transverse myelitis, optic neuritis and Devic's disease, all of which also are evaluated and treated at the UB Pediatric MS Center.

"In order for MS to be diagnosed," Weinstock-Guttman emphasizes, "there has to be at least two inflammatory demyelinating events that occur at least a month apart and affect two different areas of the central nervous system."

"If the events occur just once, they are often thought to be triggered by a viral infection and are referred to as 'monophasic' because the patient will recover and never have other recurrences.

"The monophasic events," she continues, "are commonly ADEM and usually require hospitalization. More often than not, the children recover on their own; however, we often use steroids or IV immunoglobulins to help or to shorten the recovery period."

While the recurrence of these demyelinating events is key to a definitive diagnosis of MS, Weinstock-

Guttman explains that she and her colleagues do not wait for this to happen but instead proactively monitor the children with MRI scans, which can highlight the presence of clinically silent lesions.

"We are watching very, very carefully," she says. "If the MRIs show any new disease activity or new clinical presentation, then we start therapeutic interventions."

These interventions, which have proven beneficial primarily in the adult population, include recombinant interferon products and other immune-modulating drugs, such as glatiramer acetate (used because the immune system in MS is dysregulated as seen in other autoimmune diseases).

"We begin with small dosages," says Weinstock-Guttman, "but if we see that the disease is not fully controlled, then we slowly increase to dosage levels that are used in the adult MS population."

This proactive treatment is critical to the children's long-term health because it is now understood that not only is myelin (white matter) being destroyed by the disease, but also the axons (gray matter), explains Weinstock-Guttman, who, along with other members of the center, conducted research that contributed to this finding.

Learning from Children

CHILDREN—ESPECIALLY YOUNG CHILDREN—present with MS differently than do adults, explains Ann Yeh. In particular, she says, they have more "active" cases when compared to their adult counterparts, referring to the fact that children have recurrent relapses more frequently and closer together.

In addition, they have the two distinct presentations: the chronic-relapsing, and the monophasic, which mimics MS.

"The children with monophasic events can recover remarkably well," she notes. "We can see from the MRI that the tissue goes back to being pretty much normal, although we know that the children never recover 100 percent."

"So we have much to learn from the pediatric population because there has to be a reason why some children go on to a relapsing course and some come out with just one episode and never have another."

"While monophasic events do occur in adults, they don't happen as frequently as they do in children," Weinstock-Guttman points out, emphasizing that the exploration of this difference is pivotal to research efforts for the entire Pediatric MS Network.

NEUROIMAGER ROBERT ZIVADINOV, MD, PhD, left, AND MURALI RAMANATHAN, PhD, RESEARCH DIRECTOR FOR THE CENTER

The pediatric MS population provides a unique window into MS in general, because these cases help us to understand how the genes and environment work together to potentially cause or modulate the risk of MS.

—MURALI RAMANATHAN, PhD



“We are bringing all the cases together through the network and comparing what’s happening in the immune system in these children who are able, by themselves, to close down a monophasic event, versus the ones who go on to develop MS,” she says.

These “immunological parameters” are being explored in UB’s Laboratory for MS Neuroscience located within the Department of Pharmaceutical Sciences on the university’s North Campus. The laboratory is directed by Murali Ramanathan, PhD, associate professor of pharmaceutical sciences and neurology, who also serves as research director for the UB Pediatric MS Center.

“The causes of MS are not well understood, and the treatments that are available are not cures,” says Ramanathan. “So there is a fundamental need to understand the disease process so that we can realize what constitutes a cure.

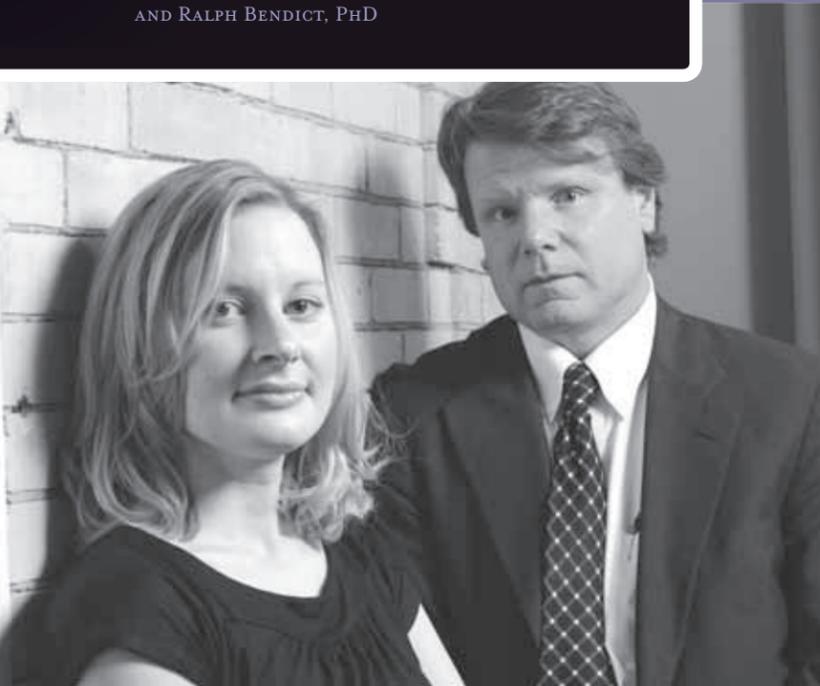
“The pediatric MS population provides a unique window into MS in general,” he continues, “because these cases help us to understand how the genes and environment work together to potentially cause or modulate the risk of MS.”

One such area of research that Ramanathan is exploring is the putative link between high rates of MS among

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—RALPH BENEDICT, PhD

NEUROPSYCHOLOGISTS JOY PARRISH, PhD,
AND RALPH BENEDICT, PhD



people who live in the 40 to 60 degree latitudes (such as in Western New York) and deficiencies of vitamin D, a hormone that is primarily synthesized in the body by sunlight. In addition, the studies are exploring possible metabolic dysfunctions resulting in vitamin D not being properly utilized by the body despite normal intake levels.

Other immunological studies involve collaborations with Kailash C. Chadha, PhD, a molecular and cellular biology researcher at Roswell Park Cancer Institute in Buffalo, who is exploring how a yet-to-be identified soluble protein works to suppress the body’s ability to secrete interferon.

“This action interferes with the body’s ability to fight viruses and different immune abnormalities,” explains Weinstock-Guttman. She reports that preliminary data from Chadha’s laboratory support the hypothesis that children whose immune systems are able to suppress this protein are those who don’t progress to MS after an initial demyelinating episode.

Views Inside the Brain

STUDIES THAT INVOLVE NETWORK-WIDE collaborations are also being conducted by the scientists in the UB Pediatric MS Center who specialize in neuroimaging and neurocognitive research.

The neuroimaging studies are focused on exploring how MRI scans can best be used to provide clear-cut diagnostic guidelines for pediatric MS, as well as how the scans can be used to more accurately predict the course of the disease once a diagnosis is made.

Because symptoms of MS in children tend to “come and go” and can mimic other neurological conditions, researchers in the field are particularly interested in discovering methods that can be used to arrive at definitive diagnoses of MS as early in the disease course as possible.

The center’s MRI studies are being led by Robert Zivadinov, MD, PhD, associate professor of neurology and director of the Buffalo Neuroimaging Analysis Center in the Jacobs Neurological Institute.

Zivadinov explains that the UB team of MRI researchers is part of a subgroup within the Pediatric MS Network that is working to establish these diagnostic guidelines. Each group—with the others being Harvard, UC San Francisco, and the Mayo Clinic—has been assigned a different set of data to collect, and then the information will be combined and analyzed.

“Here in Buffalo, we are receiving [MRI] images from all six centers in the Pediatric MS Network, and we are doing quantitative analyses of lesion-related measurements,” explains Zivadinov. “This means we are using computerized tools to automatically determine where the lesions will most likely appear—in which part of the brain or the spinal cord—what these lesions look like, and whether they are an MS lesion or a lesion that is from ADEM.”

He explains that a series of papers published by a group of pediatric MS researchers in Paris recently reported that lesions located in the corpus callosum are most predictive of the kids who will go on to develop MS but that “at the moment, in the literature, that’s the only accepted parameter we have to say, ‘Wow, this is probably a child who will have MS and not ADEM.’”

Once the first phase of research is done in collaboration with the subgroups, Zivadinov and his team are planning three additional phases, the last of which involves potential collaborations with the National Institutes of Health to tap into a database of young healthy controls that is being established there.



The neurocognitive studies at the UB Pediatric MS Center are being conducted by Ralph Benedict, PhD, professor of neurology and psychiatry, who explains that the children are given a standard battery of tests after they have recovered from an initial relapse or neurological event and then are tested every two years after that.

The questions or problems posed to the children are related to language, spatial abilities, memory, attention and “higher executive function”—the ability to think conceptually, and abstractly, and to solve problems.

Benedict and his colleagues at the center, including Joy Parrish, PhD, and Lisa Jackson, PhD, also spend time with the children and their parents in order to collect information about the patient’s history and current psychological functioning.

“Pediatric MS is something new to medicine, and there are some unique aspects to the disease that are a challenge for the neuropsychologist,” says Benedict, who in 2001 chaired an international meeting of neuropsychologists and psychologists that resulted in the establishment and publication of standard neurocognitive tests for adult MS patients.

About three years ago, Benedict began meeting with pediatric neuropsychologists with the goal of establishing a similar standard for children and adolescents based on an abbreviated version of the test for adults.

This work was successful, and the agreed-upon tests have subsequently become the standard battery now used by the centers in the Pediatric MS Network, as well as other centers.

Research pertaining to the performance of children with MS is yet to be published, but preliminary findings



JENNIFER RAY, RN, BSN, left, AND MARY KARPINSKI, LMSW

The biggest thing that patients' families tell me is that the teachers, guidance counselors and school psychologists don't believe them when they try to explain that their child has special needs. So when you don't see the needs, you don't justify efforts to accommodate them.

—MARY KARPINSKI, LMSW



PHOTOS BY JODI MILLER



suggest good reliability and predictive validity. The team is looking for abnormalities in cognitive functioning that are attributable to cerebral disease associated with this illness. Information regarding the child's actual capabilities can help the family's reaction to the disability related to the disease in general, Benedict explains.

"This is a very scary experience for these children," he says. "They have a dramatic neurologic event that they don't understand. They may be struggling in school now and have no idea why. They can become anxious and depressed, which can interfere with sleep and cause irritability, which in turn can disrupt the household and interfere with education. Some parents may not understand why their child is behaving abnormally and, therefore, use maladaptive parenting strategies.

"The neurocognitive assessments are necessary to understand the child's psychological and cognitive states," he continues, "and then we need to help the neurologists, the parents and the school system with the necessary treatments and management practices that will help the patient."

Benedict says that the work of Karpinski, the licensed medical social worker in the UB Pediatric MS Center, is key at this juncture. "She's critical. She's the captain of the team in a way because she knows what everybody else is doing, and it's her job to get this information and see that it is translated in such a way that it will help the patient and the family."

Educating the Educators

AS A PATIENT ADVOCATE AND FACILITATOR, Karpinski has her work cut out for her when it comes to pediatric MS.

"The biggest thing that patients' families tell me is that the teachers, guidance counselors and school psychologists don't believe them when they try to explain that their child has special needs," says Karpinski. "So when you don't see the needs, you don't justify efforts to accommodate them."

Further compounding the problem, she says, is the fact that about 75 percent of the schools confuse MS with other diseases, most commonly muscular dystrophy or cerebral palsy.

"I explain to them that MS is a totally different disease," says Karpinski, "but the feedback I often get is: 'The child looks fine, she's not walking around with a cane, she's not in a wheelchair, so there's nothing wrong with her.'"

Another misconception relates to fatigue, a common symptom of MS, and the fact that school personnel often interpret it as laziness.

"I hear that all the time—'Well, the kid is just lazy,'" Karpinski says. "So it's my job to explain that the children are experiencing fatigue, or problems with their medications or blurred vision or memory problems.

"Olivia is a prime example," she continues. "I've written letters and have had a lot of interaction with her school to try and get her the special education that we and her parents feel she needs."

Because of Karpinski's expertise in this type of advocacy and education, she was asked by the National MS Society to contribute to a soon-to-be published book about pediatric MS aimed at providing information to schools.

In addition to working as a patient advocate and educator, Karpinski works with families to arrange their travel and stays in Buffalo, and plans an annual Fun Day for children with MS and their families that draws attendees from all over the country. Through activities such as this, children with MS have an opportunity to meet one another and to develop their own support networks.

In all her interactions with patients and their families, Karpinski says she strives to reinforce a positive attitude and to consistently encourage the children not to let the disease overtake them.

"I constantly tell them that they need to take the diagnosis and run with it," she says, "not to let it take them over because once that happens, it's hard to bounce back."

The message appears to have been one that Olivia Ballard has taken to heart.

"The other day my boyfriend asked me how come we had been dating for over a month before I told him I had MS," recalls Olivia. "I told him it kind of slips my mind all the time."

In the end, each member of the team at the UB Pediatric MS Center will tell you that it is this kind of moxie that keeps them focused on their many goals, with no detail too small to slip their minds. **BP**

To learn more

ABOUT THE EARLY STAGES OF PEDIATRIC MULTIPLE SCLEROSIS AND THE PEDIATRIC MS CENTER OF THE JACOBS NEUROLOGICAL INSTITUTE, UNIVERSITY AT BUFFALO, CONTACT US AT PEDMS@THEJNI.ORG. THERE ARE MANY WAYS TO MAKE A DIFFERENCE, EITHER THROUGH VOLUNTEERING OR MAKING A DONATION TO THE PEDIATRIC MS CAMPAIGN. FOR MORE INFORMATION, CALL (716) 829-2773.