

Watch and Wait in Neurofibromatosis Type 1 Cases

BY DOUG BRUNK
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LA JOLLA, CALIF. — Dr. Lynne M. Bird believes the \$1,500 gene sequencing test for neurofibromatosis type 1 in children is rarely necessary because it usually does not change clinical management.

She favors a watchful waiting approach in children who present with the hallmark symptom of at least six café au lait macules that are at least 5 mm in size, “and [I] wait for the second criterion to appear,” she said at a meeting sponsored by Rady Children’s Hospital and the American Academy of Pediatrics. “I follow these children as if I already knew they had NF1, monitoring them for potential complications without doing gene testing.”

The prevalence of neurofibromatosis type 1 (NF1) is 1:3,000, making it the most common neurocutaneous disorder in children. Diagnosis is made if the child meets two of seven criteria: café au lait macules; axillary or inguinal freckling; two or more neurofibromas or one plexiform neurofibroma; optic nerve glioma; two or more Lisch nodules of the iris; a distinctive osseous lesion such as pseudarthrosis or sphenoid wing dysplasia; or a family history of the disease.

About half of cases with no family history meet criteria for the disorder by 1 year of age; 97% meet the criteria by 8 years of age.

NF1 is an autosomal, dominantly inherited disorder due to mutations in a gene on chromosome 17, which encodes the protein neurofibromin, a tumor suppressor. “Finding a mutation of the gene would also allow you to make this diagnosis,” said Dr. Bird of the division of genetics and dysmorphology at Rady Children’s Hospital, San Diego. “If you have a parent with NF1 and you can determine their mutation through genetic testing, then you can offer them prenatal diagnosis. In my experience, most parents aren’t concerned enough about passing NF1 on to their children that they would consider interrupting a pregnancy. But there are

some families that have experienced major complications associated with NF1, and they are very interested in not passing the gene on to their children.”

A study of nearly 1,900 patients with NF1 found that the features of the disease typically appear in a characteristic order, beginning with café au lait macules (Pediatrics 2000;105:608-14).

Sometimes macules are present at birth “but others will appear in the first few months of life and certainly by the first couple of years of age,” Dr. Bird said. “Typically the next feature is axillary freckling, which is usually evident in the school-age child. Lisch nodules will appear gradually after that, followed by neurofibromas as a sign that the child is entering puberty.”

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DR. BIRD

Another clue is the presence of the Riccardi sign, a tuft of hair along the back near the spine. “This sign will often be present at birth and may be there before any of the café au lait macules show up, so you will look really smart if you make a tentative diagnosis upon seeing this,” Dr. Bird said.

Optic glioma almost always appears by 3 years of age “and certainly by 6 years of age,” she said. “In addition, there is frequent thickening of the optic nerves, which is asymptomatic and doesn’t cause disease.”

A rare feature of NF1 is juvenile xanthogranuloma, which occurs in 1%-2% of cases. This skin lesion usually resolves spontaneously but is associated with an increased incidence of juvenile myeloid leukemia (JML). “When you see this you want to at least do a complete blood count and be thinking about JML, and maybe contact your local oncologist to see if they have further recommendations for monitoring,” she advised.

In most cases, the diagnosis of NF1 is made on clinical exam, including a careful evaluation of both parents. “This condition is present in 1 in 3,000 in the general population, but I don’t see anywhere near the equivalent number of kids in my clinic,” Dr. Bird said. “That tells me there is a lot of undiagnosed NF1 out there. Most par-



Café au lait macules can appear at birth or in the first months of life.



Axillary freckling is usually evident in school-age children.

ents [with NF1] are healthy; they just have spots and a few lumps on their skin.”

The way to follow children with NF1 is to see them regularly for a complete physical examination. There is no way to screen for every single complication of NF1 except by talking to families, said Dr. Bird, who is also

with the department of pediatrics at the University of California, San Diego. “Families should be told that symptoms which are not self-limited need to be brought to your attention,” she said. “If there is a symptom that hangs on, that’s nagging and doesn’t go away in a reasonable amount of time, they need to come in.”

Basic follow-up tests should include checking blood pressure and monitoring for scoliosis as well as an ophthalmology evaluation and an assessment of developmental skills. “Learning disabilities are common,” she said. “Expressive language delay is the area of development most commonly affected.”

Many parents ask Dr. Bird if an MRI of the brain and optic nerves is needed in



The Riccardi sign, a tuft of hair near the spine, is often present at birth and may precede other signs of NF1.

children who present with multiple café au lait macules. “There is no evidence that detecting optic gliomas before they’re symptomatic translates into better outcome. So you could argue that doing an MRI, which requires anesthesia, is not worth the money or the risk. I am not in the habit of getting routine MRIs. I oblige for the families who really want them.”

NF1 patients with neurofibromas have a 10% lifetime risk of developing a malignant peripheral nerve sheath tumor within one of the lesions. Signs of malignant degeneration include persistent pain, a change in texture, a rapid increase in size, or development of a neurologic deficit associated with the neurofibroma.

Dr. Bird had no relevant disclosures. ■

PHOTOS COURTESY DR. LYNNE M. BIRD AND DR. MARILYN C. JONES

Direct Ophthalmic Chemotherapy Infusion Can Save Eyes

BY MIRIAM E. TUCKER
Senior Writer

WASHINGTON — Direct intra-arterial chemotherapy in children with advanced retinoblastoma preserved the eyes in 14 children and vision in 9 eyes, according to research presented at the annual meeting of the Society for Interventional Radiology.

Without the treatment, all affected eyes would have been destined for enucleation, said Dr. Pierre Gobin, professor of radiology and neurosurgery and di-

rector of the Division of Interventional Neuroradiology at New York-Presbyterian Hospital and Cornell University, New York.

A total of 22 children aged 1 month to 10 years (median age 2 years) with advanced retinoblastoma in a total of 23 eyes underwent catheterization of the ophthalmic artery via a femoral artery approach. The children were anesthetized and anticoagulated during the procedure. The chemotherapy agent melphalan was used initially in doses of 3.0-7.5 mg, but later switched to 3.5

mg and infused in combination with topotecan over a 30-minute period. The dose was a function of the eye size, not body surface area, Dr. Gobin noted.

Eleven children had bilateral retinoblastoma, with previous enucleation of the contralateral eye in 5. Eleven had previously received intravenous chemotherapy, and 8 had undergone external beam radiotherapy. Eleven patients were treatment naive. All but one had Reese-Ellsworth stage V; the remaining patient had a stage IB tumor on the macula.

Of the 20 who completed treatment (2 are still being treated), catheterization of the ophthalmic artery was possible in 18. Eleven patients underwent three treatments, 3 had two treatments, and the rest had more treatments (up to six). There were no procedure-related complications in the total of 64 procedures. There were no hospital admissions, infections, transfusions, or other complications commonly seen with intravenous chemotherapy.

Transient skin discoloration occurred in two patients. Retinopa-

thy occurred in four patients, for whom it was determined the dose was too high and therefore was lowered in subsequent patients. An inflammatory reaction during the procedure predicted the development of retinopathy, Dr. Gobin noted.

The tumors were cured in 16 of 18 patients, with 14 able to keep the eye in place and 9 with restored vision. Treatment failed in two cases, including one in which there was tumor growth.

Dr. Gobin disclosed that he had no conflicts of interest. ■