TheNetworkEdge
The NF Network presents A quarterly research review
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# The Network Edge: Volume 4 - August 2013

***The Network Edge*** **brings you quarterly updates on the latest neurofibromatosis (NF) research and clinical advances from recent scientific publications.** ***The Network Edge*** **is organized into 'bite sized' sections by NF topic area, so you can focus in on the information that is of most interest for you.**

## *The Network Edge* Features…

- **The Bottom Line**: Each section starts with a **summary sentence** highlighting the 'take home' points from that section.

- **Highlighting Federally Funded Research**: All research identified as being either fully or partly funded by the Congressionally Directed Medical Research Neurofibromatosis Research Program (CDMRP NFRP) or the National Institutes of Health (NIH) is **tagged** CDMRP or NIH after the author name.

- **A Global NF Picture**: To keep you abreast of all NF research advances, *The Network Edge* includes publications from the United States and around the world. **Country of origin** of the research study is indicated after the author name.

- **The Network Edge Archive:** At the end of this Volume of *The Network Edge* there is a table showing topics covered by past Volumes. This should help if you wish to search for further information in *The Network Edge* archive.

## Highlights from Volume 4 of *The Network Edge*:

- **New biological markers to better predict development of MPNSTs**
- **Imaging brain structure: a new approach to measuring NF1 vision loss in NF1?**
- **A potentially helpful role for radiotherapy following NF2 meningioma surgery**
- **Café-au-lait marks may carry secrets of NF1 biology**
- **Children with NF1 have reduced brain blood flow**
- **New NF2 drug therapy shows promise**
- **Growth factor TGF-beta contributes to NF1 bone abnormalities**
- **Special considerations for surgical management of very large NF1 plexiform tumors**
- **Sleep disturbances in NF1**
- **A new mouse model for studying NF1 learning disabilities**
- **Early screening for *BRCA* mutations in women with NF1 to detect breast cancer risk**
- **Multiple-spinal-menigioma disease, a new genetic condition defined**

# The Network Edge: Volume 4 - Contents

## 1. NF2 Clinical Management

**The Bottom Line: The NF2 radiosurgery debate: weighing the benefits of cochlear implants.**

***Radiotherapy/Radiosurgery***

**Massager *et al.*** *(Belgium)* analyzed data from eighteen persons with NF2 who had received Gamma-knife 'model C' stereotactic radiosurgery for treatment of vestibular schwannoma tumors between 2001 and 2010. The average follow up time on these persons after treatment was around four and a half years. Sixteen vestibular schwannoma tumors in twelve persons were studied, and tumor growth was found to be controlled in 80% of tumors. No one receiving radiosurgery developed facial weakness, and over three-quarters of the group had preservation of hearing. This study suggests positive effects of radiosurgery in NF2.

**Lustgarten** *(Venezuela)* presented a review of publications centered on the use of radiosurgery in NF2, highlighting the fact that NF2 vestibular schwannomas are surgically challenging. These tumors are lobular, don't have an extensive network of blood vessels like other tumors and grow faster than sporadic schwannomas. They also grow unpredictably, are typically diagnosed in younger persons than are sporadic schwannomas, and tend to engulf and even invade the surrounding cochlear and facial nerves (sporadic schwannomas instead compress and displace the nerves, making them easier to remove surgically without damaging the nerves). In short, NF2 vestibular schwannomas are more challenging to manage with traditional surgery.

From a review of the literature, Lustgarten concluded that radiosurgery may help control NF2 tumor growth, but that hearing preservation outcomes are worse for those with NF2 receiving surgery than they are for those with sporadic schwannomas. He concludes with the following viewpoint:

"There is positive and negative evidence as to whether radiosurgery might have detrimental effects if used in NF2, but that when all options and risks are presented to the person with NF2 they will choose the option that best suits their needs, whether this decision is based on time commitment, cost or invasiveness of the procedure".

***Cochlear Implants***

**Pai *et al.*** *(United Kingdom)* reviewed the outcomes of cochlear implant (CI) surgeries in five persons with NF2 and two persons with a single vestibular schwannoma, conducted between 2000 and 2012. All seven persons had profound hearing loss at the time of surgery. The study monitored speech perception and quality of life after CI surgery. Three of the five participants with NF2 group achieved satisfactory speech perception, and one of the five achieved improved environmental sound and better communication ability. Importantly, however, a comparison showed that the participants with just one vestibular schwannoma gained more benefit from the CI than those with two.

## 2. NF1 Clinical Management

**The Bottom Line: Tackling surgery for very large plexiform tumors; monitoring for tumor re-growth after surgery, malignancy or infection; face transplant success update; transitioning from pediatric to adult NF1 care.**

***Plexiform Neurofibroma***

It can be difficult for surgeons to remove an entire plexiform neurofibroma, since these often grow intimately with internal organs and not all tumor tissue can easily be removed. It is important to monitor the tumor site after surgery for tumor regrowth or malignant transformation. **Nguyen *et al.*** *(United States and Germany)* examined the records of fifty-two persons with NF1, who between them had 56 plexiform tumors, and who had undergone plexiform surgery and monitoring for up to 6 years following surgery. 8% of the group (6 children and 2 adults) had residual tumor left behind after surgery that progressed and required a second surgery. Overall tumor progression rates were higher in children than adults. The most successful surgeries were done on small plexiform neurofibromas where the majority of tumor could be removed at the outset.

Very large plexiforms tumors are called giant neurofibromas, and require special management both during and after surgery. **Vélez *et al.*** *(Spain)* describe the surgical care and clinical management of a twenty-two-year-old woman with a giant neurofibroma in the lower back and buttock. The tumor has previously been de-bulked, but that surgery had led to excessive bleeding. The tumor had then continued to grow and required further surgery. The medical team imaged the tumor by MRI prior to surgery and saw that it contained an extensive network of blood vessels which placed the tumor at risk of excessive bleeding during surgery.

In the days leading up to surgery, some of the blood vessels feeding the tumor were artificially blocked by the injection of small synthetic particles (called embolization) to help limit bleeding during surgery. A surgical stapler was used to manage bleeding during surgery. These treatments significantly controlled bleeding during surgery for what proved to be a sixteen kilogram (thirty-two pound) tumor. The patient required further surgery due to wound infection, but recovered fully and within two years was able to walk without support.

The authors propose that this approach of carefully managed embolization could be a valuable tool for the treatment of giant neurofibromas. They also propose that the clinical definition of giant neurofibroma be established as one constituting 20% or more of a person's body weight.

***Face Transplantation***

The French surgical team led by Dr. Laurent Lantieri pioneered a face transplantation approach and to date have done seventeen of these procedures including two persons with NF1. **Sedaghati-Nia *et al.*** *(France)* review the team's progress to date with this technique and the challenges it still presents. Face transplantation is a lengthy surgery of fifteen to twenty eight hours. Regulating anesthesia and fluid levels during surgery is a major challenge. Multiple blood transfusions may be required due to hemorrhaging. The NF1 surgeries were particularly challenging because the entire face was being grafted, whereas for other conditions, such as burns, only part of the face needed to be grafted. In the period following surgery, the transplant recipients face challenges including opportunistic bacterial infections due to being immune suppressed. Nevertheless this pioneering technique offers promise to many including those who are most greatly affected by facial neurofibromas.

***Transitioning from Pediatric to Adult Care***

NF1 is a lifelong condition requiring ongoing medical care, and transitioning from pediatrician to adult doctor can be challenging, as highlighted by **Van Lierde *et al.*** *(Italy).* To place this in context, NF1 is a rare disease (i.e. affecting fewer than 200,000 Americans); and there are an estimated 5,000 and 8,000 rare diseases, many with childhood onset. Like NF1, many rare diseases are complex conditions and can include a learning disability, presenting challenges in securing effective lifetime services. Adult doctors are often less familiar with rare conditions than are pediatricians. In Italy, as in many countries, there are no national guidelines for NF1 pediatric-to-adult transition, and no resources to support this. This report presented a 'call to action' to advocate for our governments to address this gap. This would actually be to the government's benefit, since ignoring this issue will ultimately lead to higher costs for healthcare services in the long run.

## 3. NF1 Bony Abnormalities

**The Bottom Line: Altered bone metabolism in children with NF1; identifying clinical predictors of NF1-related scoliosis; the link between pain and spine stability in NF1; high levels of growth factor TGF-beta-1 contribute to bone abnormalities in NF1; highlighting potential orthodontic impacts of NF1**

***Altered Bone Metabolism***

Bone mineralization is reduced in people with NF1, but it is not clear why or what its impact is. **Armstrong *et al.*** *(United States and Canada)* study eighteen children with NF1 but no visible bone abnormalities, and compare them to their brothers and sisters who don't have NF1 but have a similar diet and lifestyle. All of these children were compared to a larger group of 'control' children with no family history of NF1. The children with NF1 had reduced bone mineral content in the lumbar spine and femur (leg bone), than did their siblings or the control children. The children with NF1 had reduced density of trabecular (porous) bone in the tibia (leg bone) as well as reduced bone strength and reduced resistance to bending and stress. Children with NF1 had higher levels of blood calcium (suggesting more turnover of bone) than their brothers and sisters or the controls, though this needs further investigation. However, all of the children had the same incidence of arm and leg fractures and the same Vitamin D levels. The study concluded that children with NF1 might have a specific deficit in trabecular bone metabolism, and that this might be due to a delay in puberty and production of sex hormones.

***Scoliosis***

Scoliosis, or curvature in the backbone, is the most common bone abnormality in NF1 seen in about 30% of cases. Many people will require surgery for scoliosis at some point in life, but there are no reliable predictors for when or whether this will be needed. **Lykissas *et al.*** *(United States)* searched for such predictors by examining the past medical records of fifty six individuals with NF1. 63% of the group had three or more abnormal features of the spine, and these were the individuals in greatest need of surgery. The features most likely to lead to surgery were vertebral scalloping (concave regions appear on the back of the vertebrae) and dural ectasia (ballooning of the membrane around the spinal cord). The group proposes that studying the extent of these features could potentially predict the likely need of surgery in scoliosis.

***Bone Abnormalities as a Source of Pain***

Dural ectasia mentioned above is actually quite rare in NF1. It can cause significant pain but it is not clear why. A study of four persons with NF1 and dural ectasia by **Khoo Bao *et al.*** *(United Kingdom)*

showed that around the area of dural ectasia there are stress fractures in the bone, sometimes including fractures in the pedicles, which are small bony connector structures within the backbone. It is controversial whether the dural ectasia causes these fractures or vice versa. This new study suggests that these could occur simultaneously, agitating each other. Unfortunately this is a difficult aspect of NF1 to detect and study. When persons with NF1 present with pain, the first thought by the health professional is usually that the cause is malignancy, which is evaluated through MRI or PET-CT. MRI is not optimal for evaluating bone fractures, but CT is effective, and therefore this should be kept in mind during CT imaging in a person with NF1 presenting with pain. Detecting spinal fractures early is important as these can be managed by spinal stabilization, which would help avoid future deterioration.

***Facial and Jaw Bone Abnormalities***

NF1 can affect the teeth, mouth and jaw, either during development of these structures, or later because of tumors pressing on these structures. These can affect quality of life, and present a challenge for physicians once the malformations are established. **Kopczynski *et al.*** *(Poland)* report on a nine-year old girl with NF1 related tumors in the face and salivary gland on one side. The tumors had distorted the chin toward the unaffected side of the face and affected the angle of the mouth. CAT scanning revealed that the development of the bony structures had been affected by the growing tumors. Unfortunately, the tumor continued to grow after removal, and efforts to use clinical devices to correct the abnormality were not successful. The authors highlight this case for clinicians to be aware from a very early age that children with NF1 can develop abnormalities in the face and jaw, affecting dental development as well as physical development, and suggest orthodontic check-ups be an integral part of care from the time of NF1 diagnosis so that any problems may be identified and treated as early in life as possible.

***Bone Biology***

**Rhodes *et al.*** CDMRP *(United States)* propose that hyperactivity in the cell signal transforming growth factor beta-1 (TGF-beta-1) contributes to bony abnormalities in NF1. They show that mice with NF1 bony abnormalities have blood levels of TGF-beta-1 five to six times higher than normal. High levels of TGF-beta-1 were also seen in blood taken from people with NF1 bone abnormalities. Further study showed that in the bone itself, TGF-beta-1 is made by osteoblasts, the cells that give rise to new bone; and it is these cells that over express TGF-beta-1 in the mouse bone. When 'functional' neurofibromin (NF1 protein) is re-introduced into defective mouse osteoblasts, TGF-beta-1 signaling is normalized; and when an inhibitor of TGF-beta-1 is given to the mouse model, fractures in these mice are better able to heal. These findings support a role for TGF-beta-1 in mediating the occurrence of bony abnormalities in NF1 and suggest this growth factor pathway could be a future focus for targeting drug therapies.

## 4. NF1 and the Eye: Optic Pathway Gliomas and Other Ocular Features

**The Bottom Line: Examining the brain structure to predict potential vision loss in NF1; new clinical eye features in NF1; evaluating optic nerve tortuosity; optic pathway glioma and diencephalic syndrome.**

***Clinical Eye Measurements in NF1***

**Cassiman *et al.*** *(Belgium)* discuss the importance and controversies of the ophthalmic exams done in the course of NF1 clinical diagnosis and management. These include diagnostic identification of Lisch nodules and monitoring for optic pathway glioma, sphenoid dysplasia of the bony eye socket, and plexiform neurofibromas around the eye orbit. There is some controversy around how screening and follow up for the different features is done, and this group highlights a need to improve these by better

understanding the natural history of these features. For optic pathway glioma in particular, vision is principally used as a measure of improvement in response to drug therapy, but there is no single widely used and accepted visual acuity assessment protocol.

One of the challenges is that measuring visual acuity in children can be difficult because it depends on the full cooperation of the child, who is often quite young. Seeking an alternative measure of visual acuity, **de Blank *et al.*** [NIH] *(United States)* measure brain tissue microstructure, specifically in the optic radiations, the nerve fibers that carry images from the eye to the visual cortex, the part of the brain that 'interprets' these were examined by diffusion tensor imaging (DTI) in the ophthalmology records of children with optic pathway glioma. The study showed that loss of visual acuity correlated with progressive structural changes in the optic radiations including changes in nerve fiber integrity. This brain measurement could be further refined and used to predict vision loss, so that children at greatest risk could receive appropriate clinical management.

A Japanese group recently published three papers exploring other effects in the eye that may be associated with NF1 and may serve as clinical markers. **Makino and Tampo (ref. 1, ref. 2)** *(Japan)* present a report on a thirty-five-year-old man and a twenty-year-old man, both with NF1, who came to their clinic for an eye exam but did not report vision issues. Infrared fundus autofluorescence (IR-FAF) showed these men to have multiple, bright patchy lesions in the choroid of the eye which lies behind the retina. The team suggests that these choroidal abnormalities be explored as a diagnostic tool for NF1 to use in addition to looking for Lisch nodules.

The same team, **Makino *et al.*** *(Japan),* report an unusual feature in the eye of a 30-year-old woman with NF1: abnormalities in the blood vessels of the retina. This is a rare condition in the general population, and the group believes this is the first case reported in NF1. This woman also had the choroidal abnormalities mentioned above. What was intriguing was that in monitoring this woman over a number of years, the abnormal blood vessels seemed to undergo dynamic changes. In contrast, when abnormalities in the blood vessels of the retina are seen in the general population, these remain quite static. The group will pursue this finding.

***Optic Nerve Tortuosity***

Children with NF1 often have tortuous ('squiggly') optic nerves; in the general population, the optic nerve is straighter. It is not really clear what a tortuous optic nerve means in NF1, and there has been no way of effectively measuring this. **Ji *et al.*** [NIH] *(United States)* took on this question with a goal of developing a 'tortuosity index' that could be measured from MRI images to create a universal scale. The index was developed taking into account the overall dimensions of the optic nerve. This study examined retrospective data from children captured over a period of eight years from children with NF1 who had undergone MRI imaging for tumor exams, and children without NF1 who had undergone MRI for headache evaluation. Tortuosity was greater in the NF1 group (both in those with and without a diagnosed optic pathway glioma) than those without NF1. The tortuosity index proved to be more reliable than prior methods such as visually analyzing the optic nerves and making a subjective assessment. In this study, 84% of children with NF1 were classified with tortuosity. The next step is to correlate tortuosity with vision status, optic pathway glioma status, etc. to see if tortuosity might be a predictor of other NF features.

***Diencephalic Syndrome***

Diencephalic syndrome can occur in infants and causes profound emaciation in the child. Affected children lack fat tissue under the skin, have difficulty gaining weight even when taking in normal calorie amounts, are hyperactive and may develop hypothalamic brain tumors. **Cavicchiolo *et al.*** *(Italy)* describe a case of diencephalic syndrome in a three-year-old with NF1 and an optic pathway

glioma that was initially stable but began to grow one year after diagnosis. It is believed this tumor growth impinged on the hypothalamus and resulted in diencephalic syndrome. Once the child received treatment to stabilize the tumor growth, the diencephalic syndrome subsided. The authors suggest that children with optic pathway gliomas should be monitored for symptoms of diencephalic syndrome.

## 5. Heart and Blood Vessel Abnormalities in NF1

**The Bottom Line: Brain blood flow is reduced in children with NF1; link to glaucoma in NF1; potential blood vessel rupture in NF1.**

***Blood Brain Flow***

Heart and blood vessel abnormalities can occur in NF1 and affect any region of the body. As discussed in Volume 3 of *The Network Edge,* this includes the brain where abnormal growth of brain blood vessels in children, called Moyamoya, can lead to stroke. However the full spectrum of abnormalities in brain blood flow in NF1 is not known.

**Yeom *et al.*** *(United States)* evaluated retrospective data from children with and without NF1 who had been examined between 2010 and 2012 using a specialized imaging technique called arterial spin-labeled perfusion (ASL). This provides a highly sensitive measure of brain blood flow. ASL had been used in children with NF1 to examine brain structure; and in children without NF1 it had been used for a variety of clinical investigations such as headaches or dizziness. The study included a very select subpopulation of fourteen children with NF1 aged twenty-two months to eighteen years old, and age matched children without NF1. The study excluded those with diagnosed Moyamoya, those with psychiatric problems, and those who had been exposed to chemotherapy or radiation, all of which might independently affect blood brain flow. The study found significantly reduced brain blood flow in various regions of the brain in children with NF1, not seen in children without NF1. Brain blood flow is tightly linked to the body's metabolism and the group proposes that an underlying metabolic difference in the NF1 children is undermining brain blood flow. The authors looked for a connection with learning disabilities but found none. They acknowledged this is a very small and early stage study but will explore this further.

***Structural Blood Vessel Abnormalities***

Blood vessel abnormalities in NF1 can extend to the tiniest blood vessels such as those in the eye. **Pichi *et al.*** *(Italy)* report on the case of a thirteen-year-old boy with NF1 who came to their clinic reporting pain and blurred vision in one eye, and was found to have high pressure in the eye. This had previously been described and treated as hypertensive uveitis. Imaging the boy's eye revealed tortuous blood vessels with poor flow; this was subsequently confirmed as retinal ischemia. This was finally diagnosed as neovascular glaucoma caused by the occlusion of abnormal blood vessels. This case highlights the potential for glaucoma in NF1 as a side effect of abnormal blood vessels.

**Puvanesarajah *et al.*** *(United States)* report on a thirty-two-year-old man with NF1 presenting with upper back pain, muscle weakness, numbness in the extremities and difficulty urinating. Imaging revealed a neurofibroma in the spine, and subsequent surgery showed there had been a blood vessel rupture. This turned out to be an intercostal arterial aneurysm (weakness in the wall of an artery located between the ribs). Following surgery to remove the tumor and repair the aneurysm, the man made a full recovery. This case highlights the potential for blood vessel rupture in NF1.

## 6. NF1 Malignant Peripheral Nerve Sheath Tumors

**The Bottom Line: Identifying new molecular 'predictors' of MPNST; progress in searching for new MPNST drug targets; utilizing MRI and PET together in MPNST diagnosis.**

***Molecular Markers of MPNST***

People with NF1 have a one hundred times greater risk of developing malignant peripheral nerve sheath tumor (MPNST) than do the general population; half of all cases of MPNST are seen in NF1. Early detection of MPNSTs is critical, as these are difficult to manage. In the past couple of Volumes of *The Network Edge* we have highlighted research focused on identifying markers for malignant peripheral nerve sheath tumors. The goal is to be able to predict whether a person is at risk of developing MPNSTs so they can receive the appropriate clinical management.

**Park, Sawitzki *et al.*** *(Germany and Korea)* reviewed what has been published about this field. They identified fifty-six possible blood markers for MPNST and used these to screen blood samples from one hundred and four persons with NF1, with and without MPNST, and from forty-one persons without NF1. From this study, four markers of particular interest were identified: epidermal growth factor, interferon-gamma, interleukin-6, and tumor necrosis factor-alpha. All four of these had an altered expression in NF1. Another two markers, IGFBP1 and RANTES, were elevated specifically in persons with NF1 and MPNST. These six markers were further analyzed to see whether marker level correlated with NF1 tumor load (the volume of tumors identified in an individuals' body by MRI scan). IGFBP1 was found to correlate with tumor load. The two markers IGFBP1 and RANTES may have future applications as predictors of MPNST occurrence in NF1.

Two other recent studies look at a role for miRNAs as MPNST predictors. miRNAs are small cellular elements which play a role in many normal cell functions. Certain miRNAs are elevated to unusually high blood levels in cancer.

Volume 3 of *The Network Edge* reported on the work of Weng *et al.* suggesting that miRNAs could predict whether someone with NF1 is at risk of developing MPNSTs. **Weng *et al.*** *(China)* have expanded this study and examined the genetics of two hundred persons with NF1 and one hundred and fifty six persons with NF1 and MPNST to look within eleven different miRNA signaling pathways for the presence of 53 mutations called 'single nucleotide polymorphisms (SNPs). This study confirmed that there are specific miRNA mutations which individually, or in combination, might promote the risk of MPNSTs.

**Masliah-Planchon *et al.*** *(France)* examined the activity level of three hundred and seventy seven well know miRNAs in a series of NF1 related dermal neurofibromas, plexiform neurofibromas and MPNST tumor samples and cells. The study found a variety of fluctuations in miRNA levels. Most significantly this included fluctuations in miRNAs that regulate the tumor suppressor gene *PTEN,* resulting in a drop in *PTEN* activity, which is typically associated with cancer. *PTEN* activity was at higher levels in dermal neurofibromas and plexiform neurofibromas than in MPNSTs. Identification of these miRNAs could help inform future research strategies toward predicting and treating MPNSTs.

**Rahrmann *et al.*** [NIH] *(United States)* have developed a unique approach to studying the genetic mutations underlying NF1. The group uses the 'Sleeping Beauty' transposon system which introduces small pieces of DNA randomly into the genome of Schwann cells and their precursor cells in mice. Many of these mice go on to form tumors. Studying these helps to identify which mutations may be driving MPNST development. The group studied two hundred and sixty nine neurofibromas and one hundred and six MPNSTs that grew in mice following the 'Sleeping Beauty' treatment. These revealed six

hundred and ninety five new genetic sites in the neurofibromas, and eighty seven new genetic sites in the MPNSTs, that seemed to be significant. Comparing this to human data, the group identified a number of new candidate gene mutations that could have a role in MPNSTs. In addition a new gene of unknown function, *Foxr2,* was identified. *Foxr2* turned out to be a proto-oncogene (i.e. being cancer-associated) and is increased in expression in MPNST cells compared to normal Schwann cells. When *Foxr2* is introduced into normal cells it promotes them to make tumors. *Foxr2* may have a role in maintaining growth of MPNSTs. Overall this study has turned up a number of interesting leads for future studies to identify and develop treatments for MPNSTs.

***Clinical Management of MPNSTs***

Finally, moving to the clinical imaging setting, ***Ahlawat et al.*** *(United States)* report a case of a fifty-three-year-old man with NF1 reporting progressive pain in his left leg. PET imaging revealed two masses in the thigh that were suspect MPNSTs. Anatomical and functional MRI analysis followed, and the functional MRI analysis, which examines tumor metabolism, actually suggested that the two suspect tumors had different features. Subsequently both tumors were surgically excised. One was indeed found to be an MPNST, while the other was found to be a benign schwannoma which had essentially 'mimicked' an MPNST. From this study the authors highlight the importance of using anatomical and functional MRI as well as PET when seeking to diagnose an MPNST.

## 7. NF1 Learning Disabilities

**The Bottom Line: A new mouse model for studying NF1 learning disabilities shows promise.**

**Wozniak *et al.*** CDMRP, NIH *(United States)* created a genetically-engineered mouse that is prone to develop optic pathway gliomas, and also has NF1-related learning disabilities. These mice, termed *Nf1-OPG,* have previously been shown to have low levels of the nerve signal dopamine in an area of the brain called the striatum. This was believed to be contributing to learning disabilities in these animals, since this behavior can be corrected by the drug L-Dopa, which compensates for reduced dopamine. In this study, the *Nf1-OPG* mice were subjected to maze tests and intellectual challenges. The *Nf1-OPG* mice showed a reduced wish to explore their environment, and generally moved around less, particularly when the environment was "less safe" (e.g. in a maze, when the arm of maze was 'open ended' versus closed). The *Nf1-OPG* mice also showed less interest in sniffing smells ("olfactory investigations") and were less willing to stand on their hind limbs ("rear") to reach a suspended ball. When these mice received the drug L-Dopa, these behaviors became more normalized. Future studies by the group will look at changes in signaling pathways within the brain to see if these correlate with the behavioral changes seen in the *Nf1-OPG* mice. The model certainly seems to be useful for further study of NF1-related learning disabilities.

## 8. Altered Brain Function in NF1

**The Bottom Line: Poor sleep quality for those with NF1; interpreting UBOs/T2-hyperintensities; special considerations for epilepsy in NF1.**

***Sleep Disturbances***

NF1-related sleep disturbances are not often discussed, but **Leschziner *et al.*** *(United Kingdom)* focus on sleep patterns in a study of one hundred and fourteen individuals with NF1. The study considered factors that might influence sleep, such as drugs prescribed, physical complications and employment status. Overall, those with NF1 had a poorer sleep quality and more sleep disturbances than did the general population. The study suggests this to be influenced by a number of factors including pain, anxiety, depression and learning disabilities.

***UBOs/T2-hyperintensities***

A challenge for physicians in imaging and monitoring tumors in the brain of children with NF1 is the appearance of T2-hyperintensities – also known as 'bright spots' or 'unidentified bright objects' (UBOs) - that are visible on scans. These hyperintensities usually disappear with age and are not cause for concern in kids, but they can confuse the picture of what is being visualized in the brain. The reason for UBOs appearing and disappearing is not well understood; they are not formally recognized by the NIH guidelines for NF1 diagnosis.

**Khan *et al.*** *(United Kingdom)* endeavor to better characterize UBOs, and the parts of the brain where they develop, with a view to considering whether they could be used as formal diagnostic clues for NF1. A retrospective review of twenty-two childrens' MRI scans was included. 81% of the children had UBOs, primarily in two regions of the brain: the globus pallidus, which regulates voluntary movement, and the cerebellum, which regulates balance. To a lesser extent, UBOs were found in the cerebral hemispheres and brainstem. UBOs were infrequent in children under four, but more common in children between four and twelve. UBOs were found to be twice as common in males, than in females. The UBOs did not seem to progress with age even when NF1 symptoms progressed.

## 9. Other Clinical Features of NF1

**The Bottom Line: A biological basis for kidney abnormalities in NF1; lung lesions and NF1; a rare cerebellar tumor; screening for high blood calcium may detect hyperthyroidism in NF1.**

***Kidney Abnormalities in NF1***

Kidney abnormalities in NF1 that are unrelated to tumor growth are rare. **Afshinnia *et al.*** *(United States)* report on a case of a forty-two-year-old woman with NF1 (and a strong family history of NF1) presenting with migraine. Clinical analysis revealed that she had proteinuria (protein in the urine) and focal segmental glomerulosclerosis (FSGS), both of which suggest damaged kidney structure and function. This is quite unusual in NF1 and the group believes it may be only the third such case reported. The woman had multiple tumors in the chest but no tumor growth around the kidney. There was no family history of kidney disease. Fortunately the woman responded well to treatment by the drug lisinopril. The investigators dig beyond the clinical and into the biology of this case and propose the kidney abnormalities seen may be rooted in organ development and are driven by abnormalities in mTOR signaling and MAP kinase signaling – both of which are known also to have roles in tumor growth.

***Brain Tumors***

Benign brain tumors such as pilocytic astrocytomas are frequent in NF1. Rarely, a malignant brain tumor – such as glioblastoma or anaplastic astrocytoma - will be identified. Any type of NF1-related brain tumor in a region of the brain called the cerebellum is very rare, so a malignant tumor of the cerebellum in NF1 is extremely rare. **Brokinkel *et al.*** *(Germany)* describe a very rare case of an NF1 related cerebellar anaplastic astrocytoma in a fifty-four-year-old-man. The tumor was partially resected by surgery then treated with chemotherapy. Though the man made recovery and treatment initially seemed to stem tumor growth, he deteriorated over the next sixteen months until receiving the drug levodopa. The authors believe this was a highly unique case and in scanning the literature could find only one other reported NF1-related cerebellar anaplastic astrocytoma in a nine-year-old girl.

Finally, in a continuing medical education report, **Antonio *et al.*** *(Brazil)* present a helpful chronology of the major advances made in NF1 research and clinical care from its historical identification until today, including some of the challenges that remain. (This paper is very readable and available free by looking up the reference listed below on www.pubmed.gov).

## 10. NF Genetics Update

**The Bottom Line: Special considerations for spinal NF1; examining *NF1* gene mutations in international populations; role for the *NF1* gene in pheochromocytoma in the general population; defining a new *SMARCE1* related genetic condition, multiple-spinal-meningioma disease.**

***Spinal NF1***

Spinal NF1 is a form of NF1 where the person has multiple spinal tumors on both sides of the spinal cord, on the nerve roots of the spine; tumors may affect all nerve roots. It has traditionally been thought to have only a minimal presence of the other tumor types and features of NF1 (e.g. bone abnormalities, learning disabilities). Spinal NF1 typically has a later life onset than 'full blown' NF1. Risk of malignancy or severe health issues is linked to the extent to which tumors develop around the spinal cord. A few recent publications examine this form of NF1.

As with NF1 in general, spinal neurofibromatosis can be inherited or can occur spontaneously. **Ruggieri *et al.*** *(Italy)* report on a pair of female twins aged sixteen who are monozygotic (i.e. they are identical twins arising from the same egg), as well as a fourteen-year-old boy, all of whom developed spinal neurofibromatosis. Neither the twins nor the boy had a parent with NF1. The twin girls developed spinal neurofibromatosis at age four. All three children were diagnosed because of the presence of large, symmetrical spinal neurofibromas and accompanying neuropathy (nerve degeneration and pain).

From a review of past publications, the authors believe this study has yielded some new findings. They believe this is the first reported case of monozygotic twins with spinal neurofibromatosis, and they believe age 4 to be the youngest reported diagnosis of spinal neurofibromatosis. Genetic analysis showed all three to have missense mutations in a region of the *NF1* gene called exon 39. Finally, all three had MRI-detected signal abnormalities in a region of the brain called the basal ganglia, which the authors also believe to be a unique finding.

**Burkitt Wright *et al.*** *(United Kingdom)* ask whether spinal neurofibromatosis can really be accurately diagnosed based on clinical features – as is largely currently the case - when no genetic analysis is done. An accurate diagnosis of spinal NF1 is an important issue for families since this will help

dictate clinical care plans and will hopefully mean a less severe outcome for the person than 'full blown' NF1. It is also important for family planning and genetic counseling purposes, since spinal neurofibromatosis tends to occur through multiple generations in families, but its diagnosis in later life often means someone is diagnosed after having children. The research group examined five families with spinal NF1 identified through the same neurofibromatosis clinic. These persons were found to have a broad spectrum of NF1 genetic mutations indicating that spinal neurofibromatosis can occur due to a number of different mutations. The family members also presented quite a variety of additional NF1 features: café-au-lait spots were found to be quite common and there were occasional occurrences of other tumor types such as optic pathway glioma. When these families were analyzed for genetic mutations, splice and missense mutations were found to be associated with 'strictly spinal' NF1 (and were seen in four of the five families studied) though frameshift and nonsense mutations may rarely be associated. From their studies the group proposes that if anyone is suspected to have spinal NF1 they should be subject as early as possible to a genetic analysis so that the right clinical monitoring plan and, if necessary, genetic counseling can be provided.

***International NF1 Genetics Studies***

Two recent publications looking at different international populations with NF1 review the range of mutations seen in the *NF1* gene.

**Van Minkelen *et al.*** *(The Netherlands)* presented a review of 18 years of data from almost two thousand people diagnosed clinically or genetically with NF1. The individuals studied had over one thousand different individual mutations, although definitive mutations were not identified for everyone even when there was a clear clinical diagnosis of NF1. The mutations were cross-referenced with the physical features of NF1 in each person to see if 'genotype-phenotype' links could be identified. The strongest link seen was that the presence of gene microdeletions was linked to a six-fold increase in children needing special education. The group commented that emerging genetic technologies should allow screening for novel mutations.

**Nemethova *et al.*** *(Slovakia)* report on a study of the range of gene mutations in one hundred and eight persons in the Slovakia population diagnosed with NF1. The population exhibited a range of physical features of NF1, and half had family members with NF1. Frameshift mutations were the most common type of mutation, in around 40% of the population; missense and splicing mutations were rarer, each seen only in about 10% of the population. Gene deletions and duplications made up about 6% of cases. A remaining five cases had nontypical splicing variants. Overall this represents a similar repertoire of mutations seen in other countries, except that there was a high representation of small deletions/insertions and a decreased proportion of nonsense mutations, than seen elsewhere. Hopefully this eastern European population can add to what has been seen in other countries.

***The NF1 Gene and Pheochromocytoma***

Volume 3 of *The Network Edge* reported that in a small number of persons with NF1, pheochromocytoma (an adrenal tumor type) was seen in conjunction with gastrointestinal stromal tumors (GIST, a potentially malignant tumor of the gut). Both pheochromocytoma and GIST are quite rare NF1-associated tumors but were found to co-exist in a small number of patients. In a new study, **Welander *et al***. *(Sweden)* report from a search of public gene databases that *NF1* gene mutations may actually be an important player not only in NF1-related pheochromocytomas, but also in person in the general population who develop pheochromocytoma. This finding could help increase a focus on pheochromocytoma and the role of the *NF1* gene in it occurrence.

***SMARCE1 Gene and Multiple-Spinal-Meningioma Disease***

**Smith *et al.*** *(United Kingdom)* have identified a new genetic condition, multiple-spinal-meningioma disease, due to a mutation in the *SMARCE1* gene on Chromosome 17. Like the *SMARCB1* gene, which is associated with a proportion of cases of schwannomatosis, *SMARCE1* is a chromatin-remodeling complex gene that also has a tumor suppressor function. Meningiomas are benign tumors that can occur in NF2 (50-75% likelihood over lifetime), and *NF2* gene mutations are frequently seen in meningiomas in the general population too. However meningiomas are not typically associated with either NF1 or schwannomatosis. Three unrelated individuals with a family history of spinal schwannomas were clinically diagnosed with spinal meningiomas but with no *NF2* or *SMARCB1* mutations. These persons were found to have previously unidentified *SMARCE1* mutations. This important study, published in *Nature Genetics* therefore puts a new genetic disease (and potential gene of interest in NF as well) on the map.

***Is it NF1?***

**Balikcioglu et al.** *(United States)* present a case of three African-American brothers with adrenal hypoplasia congenita, a rare inherited condition that in boys causes adrenal failure in infancy or childhood, and in later life, infertility due to gonadotropin deficiency and defective spermatogenesis. It is caused by mutations in the NR0B1 gene, which has sex-linked functions. In the family presented, the authors report the first ever case where boys with this condition also have features of NF1 or possibly Legius Syndrome. These included café au lait spots, skeletal issues, large head circumference, and freckling. However, no mutations in NF1 gene or the SPRED1 (Legius Syndrome) gene were found. This is an interesting case as it highlights the possibility of syndromes that may appear to be NF1 or Legius Syndrome but are not verified by genetic analysis.

## 11. What's New In Schwannomatosis?

**The Bottom Line: Highlighting the importance of educating radiologists about schwannomatosis.**

**Koontz *et al.*** *(United States)* provide a summary of the advances and challenges in the field of schwannomatosis. Though much has been learned about this rare form of neurofibromatosis, it remains unfamiliar to many radiologists. It is important that radiologists become educated about schwannomatosis, and how to differentiate it from NF2, because imaging plays such an important role in schwannomatosis diagnosis.

## 12. NF1 and Breast Cancer: An Update

**The Bottom Line: Early screening for *BRCA* mutations in women with NF1 may help with early detection of breast cancer risk.**

As we have reported in past Volumes of *The Network Edge,* there is a growing body of evidence that women with NF1 are at increased risk of developing breast cancer compared to the general population. **Campos *et al.*** *(Spain)* report on two women from the same family affected by both *NF1* and early-onset breast cancer (diagnosed at ages forty and thirty-five). Mutation analyses of these women identified a type of genetic mutation called a nonsense mutation in the *NF1* gene; and a type of genetic

mutation called a frameshift mutation in *BRCA1*, a gene which is closely linked to increased risk of breast cancer and which is located on the same section of Chromosome 17 as the *NF1* gene. The sisters had a family history of NF1 including a brother with an *NF1* mutation but no *BRCA1* mutation. This study suggests there may be value in early screening for *BRCA* gene mutations in women with NF1 so that any added risk of developing breast cancer can be fully evaluated and managed.

## 13. What's New in NF2 Biology?

**The Bottom Line: New tumor drug therapy shows promise.**

**Tanaka *et al.*** *(United States)* report on the candidate NF2 therapy NXD30001. This drug targets HSP90, a 'chaperone protein' in the cell whose normal role is to stabilize a range of signaling molecules involved in cell division and growth. The HSP90-regulated signals are hyperactive in NF2 tumors and HSP90 itself is expressed at higher than normal levels in a variety of tumors and tends to correlate with a poor prognosis. Treatment with the drug NXD30001 breaks down HSP90 and reduces signaling in these pathways with a goal of slowing tumor growth. NXD30001 was tested in cells lacking NF2 gene function, as well as in primary cells taken directly from human schwannoma and meningioma tumors. The drug suppressed division of these cells, and genetic analysis of the cells showed that an array of molecular targets had been inhibited. The drug also inhibited tumor growth in animal models of NF2. NXD30001 therefore represents a promising candidate therapy for NF2 tumors. The drug has been shown to effectively cross the blood-brain barrier, which bodes well for its development into a treatment.

## 14. What's New in NF1 Biology?

**The Bottom Line: Café au lait marks yield new biology leads to understanding NF1; progress in pilocytic astrocytoma biology.**

***Biology of Café au Lait Marks***

A hallmark physical feature of NF1 is *café au lait* marks on the skin. These look like very large freckles and can be quite numerous. The tan color in *café au lait* spots comes from pigment cells within the skin called melanocytes. Though these markings do not present any health concerns, their biological development is of interest to scientists, because understanding how *café au lait* spots form might tell us a bit more about the genetic causes of NF1. **Arun *et al.*** *(Canada)* examined this question using normal human melanocytes. They found that in normal cells, the NF1 gene product, neurofibromin, interacts inside the cell with microtubules (structural elements), specifically a component of the microtubules called the 'dynein heavy chain 1' (DHC). This neurofibromin-DHC interaction normally regulates the activity of pigmentation particles called melanosomes within the melanocyte. When the NF1 gene was inactivated in these cells (as it is in people with NF1), and no neurofibromin was made, the pigmentation particles become unregulated and oversized within the cell. This contributes to the appearance of *café au lait* marks. The loss of neurofibromin's regulatory activities on microtubules may well contribute to other physical features on NF1, and the authors plan to pursue this.

***Biology of Pilocytic Astrocytomas***

Pilocytic astrocytomas are the most common glial cell tumor occurring in children, and 15-20% of these cases are in NF1. These tumors are low grade, i.e. not aggressively malignant. Though they can usually be effectively removed by surgery, some of the brain regions where these tumors grow - the optic pathway, brainstem and cerebellum – can be tricky to operate on without resulting in loss of vision or another function. **Chen and Gutmann** [NIH] *(United States)* present a review of these tumors to better understand their cellular origins, biology and how they might be treated by drug therapies. The first molecular signal to be identified as contributing to pilocytic astrocytomas was the mutation of the *NF1* gene. Non-NF1 associated pilocytic astrocytomas have an abnormal signal called fusion-BRAF (f-BRAF). F-BRAF and abnormal NF1 signaling both cause over-activity of the cell signal 'mammalian target of rapamycin' (mTOR). As a result, drugs targeting mTOR are being assessed as clinical therapies for pilocytic astrocytomas. There are good mouse models of pilocytic astrocytomas which have helped these studies tremendously. For example, various candidate genes are inactivated in different brain cell populations to see if tumors arise. The local cellular environment around where tumors form is being explored for potential 'drivers' of tumor growth, which might include the influence of another cell type called microglia. (The microenvironment concept is also seen in plexiform neurofibromas where non-tumor cells called mast cells are believed to promote the growth of the tumor; this interaction has been effectively targeted in the clinic with the drug Gleevec). It may also be the case that children developing pilocytic astrocytoma have additional differences in their genome that further amplify the likelihood of these tumors developing. This summary provides a comprehensive view of progress made to date in understanding and treating the unique tumors that are pilocytic astrocytomas.

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