TheNetworkEdge

The NF Network presents a periodic research review
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The Network Edge Volume 17: Autumn, 2019

***The Network Edge* brings you regular updates on the latest neurofibromatosis (NF) research and clinical advances from recent scientific publications. *The Network Edge* is organized into "bite sized" sections by specific subtopic, so you can focus on the information that interests you most.**

The Network Edge features…

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

- 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.

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- *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.

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Highlights from Volume 17 of *The Network Edge*:

- **Breast Cancer Risk in NF1** – The risk of developing a second breast cancer (on the other side) in NF1 is elevated compared to sporadic breast cancers, and breast cancer survival in NF1 is lower. This information should be taken into consideration when considering treatment and surveillance.
- **Heart and Blood Vessel Abnormalities in NF1** – Developmental defects in heart structure and function are frequent in NF1, and may correlate with specific mutation types.
- **Malignant Peripheral Nerve Sheath Tumors (MPNST)** – While the result of a reported clinical trial is negative, new genetic targets and new imaging tools are also reported which are advancing the field of MPNST.
- **Other Clinical Features of NF1 –** A large series of patients with NF1-associated dural ectasia (outpouching of the sac that keeps the spinal fluid in place) gives insight into management strategies.
- **Quality of Life in NF1, NF2, and Schwannomatosis** – Quality of life and patient reported outcomes are discussed in plexiform neurofibromas and cutaneous neurofibromas, respectively, as well as resiliency training and quality of life measures in adults with NF2.

- **NF2 Diagnosis and Clinical Management** – Speech and swallow dysfunction are common with NF2, and it is important to consider both patient reports and test results, which don't always align.
- **Schwannomatosis Update** – Painful schwannomas secrete inflammatory cytokines, which increase sensory nerve reactivity to pain, and may be a therapeutic target for schwannoma-related pain.

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1. Breast Cancer Risk in NF1

The Bottom Line: While we know that the risk of breast cancer is elevated with NF1, we now learn that the risk of a second breast cancer (on the other side) is also substantially increased with NF1.

Risk of Second Breast Cancer Increased with NF1

The risk of breast cancer is increased by approximately four-fold among women with NF1 compared to the general community, often leading to breast cancer development at ages earlier than average. Whereas this correlation has been defined relatively recently, there remain many gaps in knowledge about the behavior and response to therapy of NF1-associated breast cancers, as well as the risk of recurrent breast cancer (even in the other breast).

In a new article by **Evans et al** (United Kingdom, Finland, Italy, Germany, France), data from five European countries were pooled to create the largest published data source to date with regard to NF1-associated breast cancer. Here, the authors studied 142 women with NF1 and breast cancer – the vast majority of whom underwent routine mammogram screening starting *after* age 50 (which is no longer consistent with published guidelines), and compared those to 335 other women who had breast cancer but no NF1 – all of whom began screening in their 30s due to family history of breast cancer. Among the patients with breast cancer and NF1, the median age of breast cancer diagnosis was 46.9 years, but the range of ages went as low as 27 years and as high as 84.3 years. The rate of subsequent development of a second breast cancer in the other breast was similar between patients with NF1 and those with a family history of breast cancer, with a rate of second breast cancer between 15% and 26% over 20 years from first breast cancer diagnosis, which was much higher than the general breast cancer population. Breast cancer-specific survival at 10 years was 64% for NF1 patients and 91% for non-NF1 patients, and overall survival was only 37% at 20 years in the NF1 group compared to 84% in the non-NF1 group. The authors hypothesize that not only might additional NF1-associated tumors and symptoms contribute to this stark difference, but also that breast cancer treatments may worsen NF1 risk for other cancers or cardiovascular disease. There was a high rate of contralateral (other side) breast cancer among patients with NF1 (4-11 times higher risk), with a 1.1% risk per year of contralateral tumor development. This is higher than the general breast cancer population risk, but lower than the 2% per year risk for BRCA1/2 mutation carriers. After 20 year survival from a first breast cancer, the risk of developing a tumor in the other breast is about 27%, raising the question of whether bilateral mastectomy should be considered at the time of first breast cancer diagnosis (similar to BRCA1/2 mutation carrier treatment).

Taken together, this article not only highlights the frequency of breast cancer in NF1 and the need for early screening, but also newly identifies increased risk of second (other side) breast cancer in NF1. Further, patients with NF1-associated breast cancer had a poorer prognosis on average than non-NF1 breast cancer patients. It should be noted that there are significant differences in screening and treatments between countries, so it remains to be seen how closely this data reflects United States based population. Nonetheless, this is incredibly important new information and should be taken into account when planning treatment and surveillance for NF1-associated breast cancer.

2. Heart and Blood Vessel Abnormalities in NF1

The Bottom Line: Congenital heart disease is common with NF1, and there may be correlations between specific types of NF1 mutation and specific heart abnormalities

Congenital Heart Disease in NF1

While there are preliminary studies of increased structural and congenital heart disease associated with NF1, little systematic evidence exists to define the rate thereof or the associated with underlying genetic changes. **Pinna et al** (Italy) studied a group of 493 individuals with NF1 who also underwent cardiac evaluations. The average age at the time of cardiac evaluation was 21 years. In breaking down the genetic abnormalities in their group, the authors report that 77% of mutations were predicted to produce a shorter-than-normal NF1 gene product (e.g. truncating mutations), while 23% had some alternative dysfunction of the NF1 gene product (e.g. non-truncating mutations). They note that these rates of mutational changes are similar to prior reports, suggesting that this group is representative of the larger NF1 population.

The authors reported an overall congenital heart disease rate of 12.6%, and provided a detailed breakdown of the various structural abnormalities identified in their group. Interestingly, 68% of patients with NF1 and congenital heart disease were female, while only 32% were male. Among patients with both NF1 and congenital heart disease, 5% of patients had a whole gene deletion, 35% had a non-truncating mutation, and 60% had a truncating mutation. Interestingly, patients with non-truncating mutations had more than a 2-fold increased rate of congenital heart disease than those with truncating mutations. Patients with whole gene deletions also had a relatively higher rate of congenital heart disease than other mutations, though this was not a statistically significant finding (perhaps because of the relatively few cases of whole gene deletion). The authors also noted correlations between particular heart abnormalities and genetic changes, and if that level of detail is required, one should consult the original article. Finally, the authors compared the rate of other NF clinical features between those patients with and without congenital heart disease and found that the only predictive feature in this group was the presence of Noonan Syndrome facial features, which predicted a much higher rate of congenital heart disease compared to patients without those facial features.

Overall, this article not only provides important background information on the rate of congenital heart disease in NF1 – raising the level of education of the NF1 community – but also makes helpful correlations between specific mutation features, clinical features, and heart abnormalities. Patients, families, and physicians should consider the possibility of congenital heart disease in the appropriate clinical scenario, and may refer to these genetic and clinical correlations when considering such.

3. Malignant Peripheral Nerve Sheath Tumors (MPNST)

The Bottom Line: A negative clinical trial provides new insights, a new gene is identified as a possible MPNST therapeutic target, and new information focuses on best imaging tools for discovering MPNST.

a. Novel Treatment of MPNST

The rate of malignant peripheral nerve sheath tumor (MPNST) development in NF1 is approximately 15%. While complete surgical resection can be curative, often the possibility of complete removal is limited based on location or stage at the time of diagnosis. Radiation therapy is used after surgery to increase the rate of disease control, but to date no chemotherapy has shown convincing additional utility.

Recently reported laboratory data has suggested that MPNSTs require active blood vessel formation to grow, and in fact that new blood vessel formation may be a means of evading effects of chemotherapies. Further, in the laboratory, treatment of mice with MPNSTs with a combination of chemotherapies targeting both cellular growth pathways and novel blood vessel formation led to prolonged survival compared to treatment with either chemotherapy alone.

In this study, **Widemann et al** [CDMRP] (United States) translated this important information from mouse models into a human clinical trial. Here, they report the results of a study using a combination of chemotherapies treating 25 adult patients with MPNSTs that either could not be surgically removed or was recurrent or metastatic. This patient group included 17 patients with NF1, while the remainder had sporadic MPNSTs, and the chemotherapies included everolimus, an oral pill taken daily, and bevacizumab, an IV infusion given every two weeks. Notably, both of these chemotherapies are FDA approved for other diseases, but have not previously been studied together for MPNSTs.

The trial was performed in two stages to verify some level of response before exposing all patients to the therapy. First, 15 patients were enrolled in the first stage and two patients had clinical benefit: one had stabilization of a previously growing tumor by 4 months of therapy, and another had a size reduction in their tumor after 2 months of therapy (though this was not seen again on subsequent scans, so the authors don't count it as a true success in their statistics). Based on an early sign of positivity, an additional 10 patients were enrolled onto the study (totaling 25 patients). In the second group, two additional patients had stabilization of previously growing tumors and also had symptom improvement.

Overall, the authors calculated a clinical benefit in a total of 3 out of 25 patients, which was only 12% of the tested population. Whereas they had set out with a goal of 20% success, they considered that this combination was not acceptable for further studies, however several important lessons were learned. First, despite the overall trial not achieving significant clinical success, there was still evidence of activity in a small group of patients with MPNSTs, and the authors will study those tumors specifically to better understand why they had a differential response. Further, this trial design was novel in that it allowed both sporadic and NF1-associated MPNSTs, and the fact that they filled all the slots and completed all required measures was indication that mixed populations can safely and effectively be studied together. In the end, the authors hope that they can continue to translate laboratory discoveries into trials of combination targeted therapies for these tumors.

b. Genomic Analysis of MPNST

Despite aggressive surgery, radiation, and chemotherapy, MPNSTs remain a very aggressive and often fatal NF1-related diagnosis. Identifying driver mutations in the genes of MPNSTs may offer new insights into the disease and new therapeutic options.

Qin et al [NIH] (United States) report their findings on the presence and function of TYK2 gene mutations in MPNSTs. To study its function, they performed testing on patient tumors, and made both cell culture and mouse models with engineered dysfunction of the TYK2 gene. They first found that TYK2 is expressed in the majority (63%) of MPNSTs compared to only 11% of benign plexiform neurofibromas, suggesting that it has specific function in the malignancy. Then, they grew a cell culture of MPNST cells and blocked TYK2 function by two different methods which led to increased MPNSTs cell death. Next, they put MPNST tumor cells into mice and observed that blocking TYK2 expression led to decreased tumor size over time.

Taken together, the authors showed that TYK2 is commonly expressed in MPNSTs, and that blocking its function reduces tumor cell growth both in a dish and in mice. This provides exciting evidence for a potential new target for therapy development in the future.

c. Imaging for MPNST

The gold standard for diagnosing an MPNSTs is examining pathology of the lesion, though often these tumors are in difficult-to-reach locations or there is a mixture of pathology within the same lesion (e.g. some areas of malignancy mixed in with other areas of benign tumors) such that a random biopsy isn't representative of the most aggressive portion of the tumor. Clinicians often use imaging as a non-invasive means of trying to better understand the nature of a lesion, though little is known about which imaging modality is the best for this.

Ahlawat et al (United States) recently reported a retrospective review of radiology findings in 55 peripheral nerve sheath tumors (19 of which were malignant peripheral nerve sheath tumors) diagnosed in 21 different patients with NF1. They reviewed traditional MRI scans, functional MRI scans (including special images called DWI and ADC), and FDG-PET/CT imaging, which combines CT scans with additional images taken after injection of a radioactive substance into the bloodstream. The authors correlated findings specific to each imaging style in an effort to calculate the predictive ability of each type of scan.

In general, the authors note that benign lesions were smaller than malignant lesions, on average. Comparing benign to malignant tumors, they noted significant differences in both the functional MRI study characteristics and in the FDG-PET/CT scan characteristics. They also noted a correlation between those two imaging modalities in a given tumor. The authors did some impressive mathematic modeling. When they adjusted functional MRI values such that every MPNST registered as malignant on the ADC scale, there was a 94% rate of correctly ruling out malignancy (e.g. no false positives) when it was not present. Similarly, when they adjusted FDG-PET/CT values to correctly detect 100% of malignancies, 83% of benign tumors registered as negative. This means that both functional MRI and FDG-PET/CT imaging are very useful for identifying MPNSTs, but that functional MRI is superior in ruling out malignancy when it is truly not there.

Although quite technical, the findings in this study are very helpful to clinicians, patients, and patient advocates when evaluating for the possibility of MPNSTs. This should not be construed to suggest that functional MRI is always the best answer, though, as several additional factors may be taken into consideration when choosing the right test for a given patient.

4. Other Clinical Features of NF1

Dural Ectasias

The Bottom Line: Most NF1-associated dural ectasias are asymptomatic, but there is nonetheless a risk of developing symptoms and requiring intervention. The outcomes and interventions are reviewed here for a group of affected patients.

Dural ectasia is a condition characterized by dilation of the dural sac in the spine, which is the thin-walled sac that holds the spine, exiting spinal nerve roots, and spinal fluid. Dural ectasia is often associated with erosion through the vertebrae or widening of normal structures at associated levels of the spine, which may increase the risk of deformity or fracture in the spine. Although the prevalence is not known, patients and providers will know that this is a common finding in NF1, and the most common location is thoracic spine. While the vast majority of cases of dural ectasia are asymptomatic – and therefore do not require treatment – particularly large dural ectasias may cause secondary problems and require treatment.

Ploster et al. (United States) report on the natural history and management strategies for a group of 37 patients with NF1 and dural ectasia. The authors divide their patients into two groups: those who were managed conservatively (n=34) and those who were managed with surgery (n=3). Among conservatively managed patients, half were asymptomatic at the beginning of their observation, but surprisingly 28% of those developed symptoms attributable to their dural ectasia over the course of an average of 6.3 years of monitoring. This means that each patient had a 2.7% risk per year for developing symptoms, which is new and important information. Also of note, 76% of the non-surgical patients had a nearby plexiform neurofibroma associated with their dural ectasia, suggestive of an underlying reason for the ectasia's existence.

With regard to surgical management, the 3 patients (8%) that underwent surgery were monitored for an average of 9.7 years. Surgeries were due to extraspinal mass effect and, although all had initial improvement after surgery, all also developed recurrent symptoms and required reoperation with spinal fluid diversion for definitive therapy. Interestingly, pathology from one of the surgical cases revealed neurofibroma infiltration into the dura, further suggestive of an underlying causative relationship for the dural ectasia, which is a novel hypothesis.

Taken together, the authors present the largest published case series of NF1-associated dural ectasias, which are a relatively common finding. Although half (or more) of patients with dural ectasia are asymptomatic, the authors provide here some evidence of longitudinal risk of developing symptoms, information on surgical management of dural ectasias, and an evidence-based hypothesis for the cause of dural ectasia development.

5. Quality of Life in NF1, NF2, and Schwannomatosis

The Bottom Line: Quality of life impairment can be measured in children with plexiform neurofibromas and adults with skin tumors, and can be positively impacted in adults with NF2 and hearing loss through a video-chat based training program.

a. Measuring Quality of Life in Children with NF1 and Plexiform Neurofibromas

Having accurate, reliable measures of patients' symptoms and quality of life is critical for determining whether treatments in clinical trials are effective. Patient-reported outcomes (health information reported directly by a patient, often using survey questions) are one of the best ways to understand whether treatments have an effect on patients' overall quality of life and wellbeing. However, before patient-reported outcome measures can be used in clinical trials, we need to know that we're measuring the most relevant and important factors that determine quality of life.

In a prior study, Lai et al. interviewed kids with NF1, their parents, and NF clinicians to determine what the most important aspects of quality of life were when thinking about treatments for plexiform neurofibromas. The interviewees rated pain, physical functioning, social functioning, emotional distress, and stigma as the most important domains to assess for people with plexiform neurofibromas. Based on this input, **Lai et al.** (United States) picked multiple patient-reported measures corresponding to each of these domains to test further in children with NF1 and plexiform neurofibromas. They picked these measures from large databases of measures (called PROMIS and Neuro-QOL) that have already been rigorously developed and tested in a national sample of children from across the U.S.

140 children with NF1 and plexiform neurofibromas, ranging in age from 8 to 17 years old, participated in the study. Participants were recruited from a wide variety of NF organizations, including the NF Network, NF Upper Midwest, NF Midwest, NF California, NF Northeast, NF Mid-Atlantic, NF Central Plains, NF Michigan, NF Arizona, and others. Each child took quality of life surveys to measure pain interference (how much pain interferes with doing activities); upper extremity functioning, mobility, and fatigue; relationships with peers; anxiety, depression, stress, positive emotions, and sense of meaning and purpose in life; and stigma. Parents were also surveyed about their children's clinical features of NF1 and overall physical and mental health.

Children in the study had plexiform neurofibromas in a wide variety of body locations, and 54% had received some kind of treatment for their plexiform neurofibroma. 74% of parents reported their kids had learning difficulties and 48% said their kids had attention problems. Since learning and attention issues are common in NF1, it was helpful that the quality of life surveys used in this study were short and easy to understand. The researchers found that overall, kids with NF1 had worse scores than kids in the national U.S. sample on all the measures except fatigue and pain interference. The measures could accurately distinguish children with different levels of health (as reported by their parents), suggesting they are accurate measures of quality of life. Overall, these results show that these patient reported measures might be useful in clinical trials of treatments for plexiform neurofibroma.

b. Coping related to skin-related QOL and psychological distress in NF1

As stated above, patient-reported outcomes are one of the best ways to understand how a disease and any potential treatments affect a person's overall quality of life and well-being. However, many patient reported-outcomes used in NF research have only been tested in English-speaking individuals.

Previously, Bottesi et al. developed a new quality of life measure focused on skin and the effects of skin disease, called the Padua Skin-Related Quality of Life Questionnaire (PSRQ). This measure, developed in Italian, has 50 questions across 4 main topic areas: physical distress and impairment (such as difficulty playing sports or other activities); interpersonal impairment (such as difficulty in social situations or intimate relationships); negative feelings and emotions (such as feeling sad or frustrated); and positive feelings and emotions (such as feeling attractive or confident). The authors specifically included positive feelings and emotions in the measure to better detect potential improvements in quality of life after treatment.

In this study, **Bottesi et al.** (Italy) gave the PSRQ measure to 72 adults with NF1 getting care at their NF clinic at the University Hospital of Padova in Italy. Patients also completed a variety of other validated measures of their quality of life, psychosocial stress, and coping mechanisms. Doctors rated the severity of patients' NF symptoms and details about the number and location of their cutaneous neurofibromas.

The study found that people with more cutaneous neurofibromas (defined as >50 tumors by the authors) and tumors spread over more of their body reported lower quality of life on 3 of the 4 scales of the PSRQ: physical impairment, interpersonal impairment, and negative feelings and emotions. This suggests that while the positive feelings and emotions scale might help track changes over time in skin-disease related quality of life, it might not be good at distinguishing people with NF1 and different levels of cutaneous neurofibroma burden. The authors also found that people who coped with stress by trying to avoid it had lower self-esteem, more symptoms of anxiety and depression, and lower skin disease-related QoL. For this reason, the authors suggest that individuals with NF1 and a high burden of cutaneous neurofibromas may benefit from psychological counseling focused on developing better coping strategies for stress, so that they can be more confident in their ability to cope with the effects of NF1.

c. Resiliency Training and Quality of Life in NF2 (with CART)

In Volume 13 of the Network Edge, we shared results from a randomized trial by Vranceanu et al. which compared two stress management interventions delivered via group video-chats. This trial showed that a program called the Relaxation Response and Resiliency Program (3RP) may be effective at improving quality of life for adults with NF1, NF2, and schwannomatosis. However, because the video-chats relied on spoken discussion among participants, adults with NF2 who had significant hearing loss were unable to participate in that trial.

To address this gap in services, Vranceanu and colleagues adapted the same two stress and symptom management programs to be compatible with real-time captioning using Communication Access Real-time Translation (CART) services. **Funes et al**. (United States) share the results of the first randomized clinical trial comparing these two interventions for people with NF2 and significant hearing loss.

45 people with NF2 participated in the trial. Both interventions consisted of eight, 90-minute group sessions led by a clinical psychologist. Participants could log into the sessions from home using the free videoconferencing software Skype. Half of the participants followed the curriculum from the 3RP, which focused on skills to increase relaxation, mindfulness, coping with stress and uncertainty, and positive thinking. Half of the participants followed the curriculum from a more general health program, which focused on educational information about NF2 and hearing loss and strategies for healthy eating, exercise, and sleep.

Results from the trial showed that participants in the 3RP program had greater improvements in quality of life related to their physical symptoms, psychological health, and interactions with their environment than participants in the general health education program. These improvements in of quality life were still evident 6 months after the program ended. Based on these results, the researchers find that videoconferencing with CART is a useful method for providing psychosocial support to patients with NF2 and hearing loss. They recommend additional research to assess longer-term benefits of the 3RP program and to test whether different psychologists can be trained to deliver the program.

*Disclosure: The author of this newsletter is also a co-author on the paper by Funes et al.

6. NF2 Diagnosis and Clinical Management

The Bottom Line: Speech and swallow dysfunction are common with NF2, and patient reported symptoms may not always correlate with test results. Further, patients may recover from these symptoms, especially if they follow a neurosurgical procedure.

Swallowing and Speech in Patients with Neurofibromatosis 2

Difficulty with speech and swallow are common problems with NF2, largely related to tumor location. In fact, in Volume 15 of the Network Edge, we reported on a survey of patients with NF2 in which 35% of respondents reported voice handicap and 50% of respondents reported swallow dysfunction.

In their new study, **Rajendran et al** [NIH] (United States) report on 168 patients with NF2 who were evaluated with imaging and clinical exams. In a self-reported questionnaire, 33% of patients reported speech and/or swallowing difficulty. All of those patients who reported such difficulty then underwent a modified barium swallow (an X-ray test that takes pictures of the mouth and throat while swallowing to show evidence of dysfunction), and only 18% had abnormal swallowing and only 4% had aspiration (when food or liquid went into the trachea or breathing pathway). Importantly, two patients had abnormal swallows on modified barium swallow within one week of a neurosurgical procedure and both recovered to independent swallowing status. The authors did find a correlation between the presence of

dysarthria and tongue deficits and tumors associated with the hypoglossal canal (the location in the base of the skull through which the nerve to the tongue travels).

On the whole, this study confirms not only the relatively high proportion of patient-reported speech and swallow difficulties with NF2, but interestingly shows a much lower proportion of patients with abnormal swallow studies when tested with a modified barium swallow (the gold standard for swallow evaluation). The authors also found abnormal function of the hypoglossal (tongue) nerve even in patients who did not have prior neurosurgical procedures, which correlates with both speech and swallow function. This study emphasizes the importance of patients discussing speech and swallow symptoms with healthcare teams, and the fact that symptoms may not correlate perfectly with test results but are of equal importance. It also highlights the ability of patients to adapt and compensate for deficits such that swallow studies may remain or return to normal despite dysfunction and/or surgery.

7. Schwannomatosis Update

The Bottom Line: Painful schwannomas secrete certain substances that impact sensory nerves by changing their genetic expression and increasing their reaction to pain. This may lead to a targetable treatment option for schwannomatosis-associated pain.

Pain in Schwannomatosis

The majority of patients with schwannomatosis report chronic pain. The cause of pain in this disease is not clear, as some tumors may be painful while others are painless, and some patients have pain localized to tumors while others have whole-body pain. This often-debilitating pain may not be adequately alleviated with pain medications in many cases. There is a large-scale effort ongoing to understand the mechanism of pain in patients with schwannomatosis in hopes of finding better therapies.

In their new study, **Ostrow et al** FREE (United States) report on a series of experiments that advance our understanding of schwannoma-associated pain. They took surgically removed schwannoma specimens from patients and grew them in a dish in the lab, categorizing the samples based on the degree of pain reported by the patient from whom they were taken. Then, they removed the culture media (the liquid that cell cultures are grown in) and placed it on cultures of sensory nerves, trying to determine if there were any substances in the media that were secreted by the schwannomas that may impact nerve cells. Interestingly, they found that culture media from painful schwannomas caused nerve cells to have increased activity to pain-inducing chemicals compared to culture media from non-painful tumors. Painful tumor media also increased genetic expression of pain related genes in sensory nerve cell cultures, which was not seen when non-painful tumor media was applied. They presumed that the painful schwannomas were secreting substances into the culture media that exerted these effects, and so began to investigate those secreted proteins. They measured cytokines (well known inflammatory proteins) in the culture media and found greater levels of secretion from painful than non-painful tumors, which they propose may relate to the differences in sensory nerve response (and therefore pain).

Summed up, this work suggests that painful schwannomas secrete inflammatory cytokines and potentially other substances which increase the responsiveness of sensory nerve cells to painful stimuli. In contrast, non-painful tumors secrete significantly fewer cytokines. Further, painful tumor secretions increase certain pain-related genetic expression in nerve cells that is not seen from non-painful tumors. Through this work, the authors have identified several potential secretions and signaling pathways that may ultimately be suitable for targeted therapy for the treatment of schwannomatosis-associated pain.

References

Ahlawat S, Blakeley JO, Rodriguez FJ, et al. Imaging biomarkers for malignant peripheral nerve sheath tumors in neurofibromatosis type 1. *Neurology* 2019

Bottesi G, Spoto A, Trevisson E, et al. - Dysfunctional coping is related to impaired skin-related QoL and psychological distress in Neurofibromatosis type 1 patients with major skin involvement. *British Journal of Dermatology*. July 2019

Evans DGR, Kallionpaa RA, Clementi M, et al. Breast Cancer in Neurofibromatosis 1: Survival and Risk of Contralateral Breast Cancer in a Five Country Cohort Study. *Genetics in Medicine* 2019

Funes CJ, Mace RA, Macklin EA, et al - First report of quality of life in adults with neurofibromatosis 2 who are deafened or have significant hearing loss: results of a live-video randomized control trial. *Journal of Neuro-Oncology* 2019

Lai JS, Jensen SE, Charrow J, et al - Patient Reported Outcomes Measurement Information System and Quality of Life in Neurological Disorders Measurement System to Evaluate Quality of Life for Children and Adolescents with Neurofibromatosis Type 1 Associated Plexiform Neurofibroma. *The Journal of Pediatrics* 2019

Ostro KL, Donaldson KJ, Caterina MJ, et al. The Secretomes of Painful Versus Nonpainful Human Schwannomatosis tumor Cells Differentially Influence Sensory Neuron Gene Expression and Sensitivity. *Scientific Reports* 11 Sept 2019.

Pinna V, Daniele P, Calcagni G, et al. Prevalence, Type, and Molecular Spectrum of NF1 Mutations in Patients with Neurofibromatosis Type 1 and Congenital Heart Disease. *Genes* 2019

Polster SP, Dougherty MC, Zeineddine HA, et al. Dural Ectasia in Neurofibromatosis 1: Case Series, Management, and Review. *Neurosurgery* 2019

Qin W, Godec A, Zhang X, et al. TYK2 promotes malignant peripheral nerve sheath tumor progression through inhibition of cell death. *Cancer Medicine* 8 May 2019

Rajendran S, Antonios J, Solomon B, et al. A prospective evaluation of swallowing and speech in patients with neurofibromatosis type 2. *J Neurol Surg B* 2019

Widemann BC, Lu Y, Reinke D, et al. Targeting Sporadic and Neurofibromatosis Type 1 (NF1) Related Refractory Malignant Peripheral Nerve Sheath Tumors (MPNST) in a Phase II Study of Everolimus in Combinatiton with Bevacizumab (SARC016). *Sarcoma* 2019.

The Network Edge Archive

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NF Genetics Update				X	X		X	X		X	X						
Pheochromocytoma in NF1			X							X							
Social Challenges in Neurofibromatosis					X	X	X	X	X	X	X		X		X	X	
NF1 and Autism					X			X			X					X	
REiNS Collaboration Update					X								X				
Quality of Life in NF1, NF2, and Schwannomatosis												x	X	X	X		X

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