The Network Edge Volume 15: Winter, 2017

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.
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Highlights from Volume 15 of The Network Edge:
- NF1 Quality of Life and Mental Health: Children with NF1 have high rates of emotional distress and negative effects on quality of life, and newly validated questionnaires may identify patients with these symptoms, who would benefit from intervention.
- Optic Pathway Gliomas in NF1: Mutations in the front part of the NF1 gene (especially those that prematurely stop NF1 protein production) are associated with a higher risk of optic pathway glioma development.
- Optic Pathway Gliomas in NF1: Only 15% of optic pathway gliomas required treatment in a recent study, and most were treated due to vision impairment. No optic pathway glioma found incidentally on MRI (e.g. without symptoms) required treatment.
- Malignant Peripheral Nerve Sheath Tumors: NF1-associated MPNSTs tend to develop earlier, have more severe symptoms, and worse outcomes than sporadic MPNSTs.
- NF2 Malignancy Potential: Among patients without prior irradiation, no malignant peripheral nerve sheath tumor or malignant glioma was found in a large database of patients with NF2.
- NF2 symptoms: Voice and swallow dysfunction occur in 35% and 50% of patients with NF2, respectively. These symptoms affect quality of life and should be discussed with physicians in case of opportunities for therapy.
• **Schwannomatosis Update**: New insights on the genetic sequence of events that cause schwannomatosis were reported, and a new strain of mouse that mimics the actual human disease was created.

• **Communication with Medical Teams**: Evaluating a patient or family’s ability to understand medical information may improve communications with healthcare team.
1. **NF1 Quality of Life and Mental Health**  
   a. Evaluating psychosocial functioning, quality of life and distress  
   b. Longitudinal development of emotional and behavioral problems  

2. **Optic Pathway Gliomas (OPGs)**  
   a. Risk Factors and Symptoms  

3. **Malignant Peripheral Nerve Sheath Tumor (MPNST)**  
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   a. Mutational timing determines tumor syndrome type  
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1. Measuring Quality of Life and Mental Health Factors in NF1

The Bottom Line: New screening tools have been validated to effectively identify children and adolescents with impaired psychosocial function or negative quality of life, in order to provide early and meaningful intervention.

a. Evaluating Psychosocial Functioning, Quality of Life and Distress in Children and Adolescents with Neurofibromatosis Type I

Neurofibromatosis Type I (NF1) significantly increases the risk for distress and decreased quality of life in children and adolescents. While addressing symptoms of distress and following trends in quality of life are important aspects of NF1 care, a reliable tool for measuring psychosocial stress does not exist to date. Two recent studies sought not only to address the impact NF1 has on the psychosocial functioning of children and adolescents, but also to validate tools for measuring these symptoms and quality of life.

Cipolletta et al. (Italy) sought to analyze the psychosocial functioning, quality of life, and self-image of children and adolescents with NF1. To do so, they recruited 240 individuals, equally split among four groups: children with NF1, children without NF1, parents of children with NF1, and parents of children without NF1. The children filled out a self-administered Psychiatric Scales test and a human figure drawing test, while parents completed a Child Behavior Checklist. The study found that the NF1 group reported significantly higher anxiety, poorer quality of life, and children had distortions in self-image. The parents of children with NF1 were also significantly more worried about their children’s quality of life, social skills, academic performance, and attention span. This study demonstrated the impact of NF1 on quality of life and psychological wellbeing for both children with NF1 and their parents. This highlights not only the importance of including parents in future studies of this life-altering disease, but also in objectively measuring and tracking psychological symptoms and quality of life in affected families.

Wiener et al. NIH (United States) focused not only on symptoms of distress in youth with NF1, but also on identifying a screening tool that could be easily incorporated into existing scheduling for patients and would allow physicians to quickly identify at risk individuals. To accomplish this, the authors utilized the Distress Thermometer (DT), Children’s Depression Inventory, and Brief Symptom Inventory to determine their general usability and to correlate scores between pediatric patients, caregivers, and medical providers. A total of eighty youth between the ages of 7-21 with NF1 completed the scales and checklists. The results demonstrated that the DT and accompanying checklists are an effective means of identifying distress in youth with NF1 in a clinical setting, and that can be feasibly completed in an existing
appointment time. Further, the study demonstrated significant differences between ratings and symptoms reported by patients and caregivers, highlighting the importance of assessing patients themselves, rather than relying purely in caregiver input. Overall, the DT and problem checklist are an effective tool in identifying distress in this patient population, and may be considered to include in routine pediatric NF1 patient visits.

b. Longitudinal Development of Emotional and Behavioral Problems Throughout Childhood in those with NF1

Understanding the natural development of behavior, intelligence, and language development for individuals with NF1 informs medical providers on proper screening, disease prediction, and intervention strategies if problems arise. Rietman et al. (Netherlands) published a longitudinal study of children with NF1 in order to better understand the rates and outcomes of problems in these areas. The authors first assessed individuals at preschool age, and evaluated language skills, intelligence, and emotional or behavioral problems as reported by the patient’s parents. Then, they performed a second assessment when the child was in school (average follow-up time was 4.5 years) and evaluated intelligence, and emotional or behavioral problems as reported by the patient’s parents and teachers. Baseline and secondary assessments were then compared for a total of 23 patients with longitudinal data available on behavioral problems. They noted that there was no correlation between internalizing issues (negative inward-facing issues such as social withdrawal, bodily complaints, anxiety or depression) and either intelligence or language development. However, baseline internalizing problems were associated with increased internalizing problems at the second time point. This implies a longitudinal and potentially progressive nature to internalizing problems in children with NF1. The results of this study should be interpreted with caution, though, given their small population and significant dropout rate of respondents (from an original study cohort of 61 patients).

2. Optic Pathway Gliomas in NF1

The Bottom Line: Substantial work has been published recently on risk factors, clinical indicators, and outcomes for optic pathway gliomas. While consideration of this diagnosis is at the forefront of every NF1 practitioner’s mind, the data outlined here contributes to medical teams’ understanding of these tumors and will inform appropriate evaluation for patients.

a. Risk Factors and Symptoms

Optic pathway glioma (OPG) is the most common central nervous system tumor in children with NF1. It is a relatively slow-growing tumor that originates in or around the optic nerve, which transmits information from the eye to the visual network in the brain. As an optic pathway glioma develops, pressure on the optic nerve can hamper visual acuity, and a small proportion of affected children may lose vision completely. Due to their proximity to the hypothalamus and
pituitary gland (structures in the brain responsible for hormone secretion), OPGs often impact children’s hormone levels, appetite, and sleep. Recent publications have explored the risk factors relating to genetics, as well as some of the warning signs of optic pathway gliomas.

A paper by Anastasaki et al., FREE NIH (United States) explored the correlation between mutation location and type in the \( NFI \) gene and the risk of OPG development. The authors combined their own cohort of 37 patients with NF1 with four previously published NF1 data sets, and analyzed genetic and tumor data from a total of 310 individuals with NF1. The primary finding of the study was that children with NF1-associated gliomas were significantly more likely to have mutations in the 5’-end (front end) of the \( NFI \) gene than later in the gene. Secondly, they additionally identified that mutations that stop NF1 protein synthesis (e.g. truncating or nonsense mutations) in the 5’-end have a further increase in association with glioma development, although this finding was not sufficiently strong to be predictive, per se. The study’s results are significant not only in their correlation of gene mutation and patient disease, which may help physicians with predicting glioma risk and strategies for screening, but also they are among the first to find a true genotype-phenotype correlation in NF1. Although other diseases caused by mutations in a single gene often have such correlations, NF1 is notoriously difficult to predict even between generations with the same mutation, and this study has broken that mold by providing a clinically relevant genetic correlation.

In another paper by Cambiaso et al. (Italy), researchers investigated the impact of OPGs on growth hormone (GH) levels. Sixty-four children with NF1 and OPG were evaluated for accelerated growth velocity, GH levels, and for evidence of precocious (early) puberty. They found that 10.9% of the group demonstrated excess levels of GH, and two of those individuals had associated precocious puberty. Further, all children with excess GH levels had a tumor in the chiasm, a midline structure behind the eyes. This study is important not only for providing an estimate of the frequency of GH excess and precocious puberty in children with NF1-associated OPG, but also for identifying that chiasmal tumors are particularly high risk for such. Given the specific hormonal treatment and follow up necessary for GH excess, such findings are important and should be considered by practitioners. Further, the authors identified patients at risk of GH excess through observing changes in height velocity, and suggest that an excessively fast growth rate (>2 standard deviations) should warrant an MRI of the brain regardless of ophthalmologic evaluation.

Finally, in an effort to study risk factors and behavior of OPG, Trevisson et al. (Italy) studied the charts of 414 consecutive patients who were referred to their clinic for NF1 care before the age of 6 years. The average follow up time for patients was nearly 12 years. Nearly 45% of patients underwent a brain MRI in this study, of those two-thirds were performed for either neurological or ocular symptoms, and one-third were screening MRIs. They first identified that about 15% of patients in this group developed OPG by the age of 15 years, which is consistent with prior reports. They interestingly determined that females had a significantly higher incidence of OPG than males. Only about 15% of patients who developed OPG were treated – mostly for visual symptoms – while the rest were observed conservatively. OPGs were more than twice as likely to be found on MRIs performed for a clinical indication than for screening.
purposes, and none of those OPGs found on screening MRIs had visual decline. Further, location of OPG did not correlate with the risk of vision decline. Overall, this study not only confirms the risk of OPG at or around 15% by age 15, but also provides reassurance that screening MRIs for asymptomatic patients are not necessary as an incidentally identified tumor is unlikely to cause symptoms or require treatment.

3. Malignant Peripheral Nerve Sheath Tumors (MPNST) in NF1

The Bottom Line: New research has identified key differences in clinical characteristics and outcomes for NF1-associated MPNSTs compared to sporadic MPNSTs, and has determined two potential therapeutic targets in these tumors, opening up opportunities for more focused research and potential clinical trials down the road.

Malignant Peripheral Nerve Sheath Tumor (MPNST) is a type of cancer affecting the lining (sheath) of nerves. Approximately 10% of individuals with NF1 will develop MPNST in their lifetime, which arise from existing plexiform neurofibromas. MPNSTs are often aggressive tumors with a high rate of local reoccurrence and metastasis. Recent studies have aimed to better understand how and why MPNSTs present, and to investigate specific genetic contributions to MPNST growth.

b. NF1 vs Sporadic MPNST

A study by Hwang et al. (Korea) investigated the differential outcomes and clinical features of sporadic MPNST (sMPNST) versus those associated with NF1 (NF-MPNST). Their principle finding was that NF-MPNSTs presented at an earlier age (32 vs 45 years old), with a larger size (8.2 vs 5.0 cm), and required significantly more surgeries than sMPNST. The 10-year survival rate was also significantly lower in NF-MPNST (45% vs 60%), and factors affecting overall survival included extent of surgical resection, pathology grade, and presence or absence of metastasis. Overall, this study highlights the importance of maintaining a high index of suspicion for MPNST in the setting of NF1 in order to identify and treat them as early as possible.

b. Genetic abnormalities and therapeutic targets in MPNST

Additionally, two studies were recently published on genetic contributions to MPNST growth, and exploring some related treatment options. Capitalizing on recent molecular studies from mouse MPNST models, Amirnasr et al. (Netherlands) tested whether inhibition of the genes BRD4, EZH2, and TOP2A served as an effective therapy for MPNST treatment. Although inhibiting BRD4 and EZH2 expression had no effect on cell proliferation in the lab, they did find that MPNSTs overexpressing the gene TOP2A can be effectively controlled in the laboratory with the chemotherapy doxorubicin. However, this drug is already used for MPNSTs in clinics and is effective only a fraction of the time, which the authors hypothesize may be the case only for TOP2A-overexpressing tumors. Throwing a wider net, Kolberg et al. (Norway) performed a drug screen of nearly 300 compounds on an array of MPNST cell lines and Schwann cell lines, in order to find an effective therapy. They observed a relatively strong anti-
tumor effect from medications that inhibit the gene PLK1 (i.e. volasertib and BI2536), as well as from the already-available chemotherapy gemcitabine. They also identified that PLK1 was expressed in larger quantities in MPNST cell lines than in regular Schwann cell lines, and that higher levels of PLK1 expression correlated with worse outcomes. Together, these findings highlight a couple potential molecular therapeutic targets that are overexpressed in MPNSTs compared to normal tissues, and demonstrate a negative effect on tumor cell growth when inhibited.

4. NF2 Clinical Management

**The Bottom Line:** New researchers has focused on the risk of malignancy in NF2, an exploration of symptoms and quality of life in NF2, and the risk of having an underlying genetic disease for young people presenting with single meningiomas or schwannomas. Further, a validated scoring system may provide prognostic opportunity between genetic mutations and patient outcomes.

Although NF2 as a disease has been described for many decades, large holes still exist in our understanding of disease symptoms, signs, and progression. In part, this knowledge gap reflects the relative rarity of NF2, as well as the relatively slow nature of disease progression. Investigators continue to study the rates of certain tumors, the effects of the disease on disability and quality of life, and the association between gene mutation and patient symptoms.

a. NF2 Population Characteristics

A study published by Iwatate et al. (Japan) reviewed records for 807 patients with NF2 in Japan to better understand disease severity and disability for a large population. Using the Japanese NF2 Disability Scoring System – a scale from 0-25 that assigns disability values to signs and symptoms of NF2 including hearing loss, facial weakness, slurred speech, and others – the group identified that 6.1% of patients had noteworthy progression of disability (≥5 points) over the 5 year study period. In reviewing patient characteristics, they determined that the risk of progressive disability was significantly increased by receiving an NF2 diagnosis before 25 years old, a positive family history of NF2, a history of NF2 tumor-directed treatment such as surgery or bevacizumab, hearing loss, facial weakness, blindness, and weakness on one side of the body. Many of these risk factors are not surprising, as a family history of NF2 omits the possibility of mosaic disease (where only part of the body has the NF2 mutation), and early diagnosis or treatment of NF2 naturally reflects a more severe disease course. On the whole, this study highlights the varied clinical features and disease courses for patients diagnosed with NF2, and more reassuringly shows that only a small proportion of patients have a rapidly progressive course when measured by the Japanese NF2 Disability Scoring System. However, it is worth mentioning that this scoring system provides only a superficial overview of potentially severe and life-altering symptoms, and so may not generalize to every patient’s NF2 experience.

To better understand laryngeal and pharyngeal function, Best et al. (United States) used validated survey tools evaluating both voice and swallow function in a group of 40 patients with NF2. Voice handicap was reported in 35% of respondents, and swallow dysfunction was reported in 50% of respondents. The researchers went on to perform laryngoscopic examinations (using cameras to visualize the throat and voice box) on 31 of the included patients, and found 71% had impaired motion of the vocal folds and 44% had impaired vocal cord function. They also found significant associations between vocal fold motion impairment and both voice-associated quality of life and swallow-associated quality of life. Finally, the authors identified a strong correlation between vocal cord dysfunction and prior surgery in the region of the cerebellopontine angle on the same side (where the hearing and facial nerves exit the brainstem).
Overall, this study is a nice union of patient-reported symptoms, patient-reported quality of life, and physician-reported examination findings. This study should prompt early and frequent discussion of voice and swallow in patients with NF2, as well as their impact on patient function and quality of life.

In search of a better understanding of risk of malignancy with NF2, King et al. (United Kingdom) sought to study the rates of malignant transformation of vestibular schwannomas into malignant peripheral nerve sheath tumors (MPNST) in patients with NF2. Using a database of 1,253 patients with a confirmed diagnosis of NF2 from multiple European countries, followed for an average of 8.92 years per patient, the authors searched for all cases of MPNST in this population. Fortuitously, there were no spontaneous (unprovoked) cases of MPNST identified in this large group of patients with NF2. Note that this information stands in contrast to another recent report by Carlson et al. (United States) where the authors used the Surveillance, Epidemiology, and End Results (SEER) database to search for MPNSTs in the vestibular nerves for patients who never received radiation. They found that spontaneous vestibular nerve MPNSTs do occur, but only at about a rate of 1 spontaneous MPNST per 1000 benign vestibular schwannomas. Based on this, and the inherent limitations of database research (which is primarily incomplete or inaccurate documentation which cannot be verified), King et al suggest that larger populations and longer follow up may be necessary to definitively rule out spontaneous MPNSTs for patients with NF2. Importantly, King et al did find two cases of MPNST in their database, though (one was biopsy-proven and one was presumed to be malignant based on aggressive nature), but both of these cases occurred in tumors that had previously been treated with stereotactic radiosurgery (focused, high-dose radiation). Overall, these studies show low (or maybe even no) risk of spontaneous malignant transformation of vestibular schwannomas, but underline a slightly increased risk of malignant transformation (~1%) after SRS treatment of a vestibular schwannoma. This information should be taken into account when determining patient-specific therapies.

Finally, King et al (United Kingdom) published a second paper investigating the risk of malignant primary brain and spine tumors (high-grade gliomas) using the same database of 1,253 patients with confirmed NF2. Similar to the previous study of MPNSTs, the authors found no spontaneous malignant gliomas in this population. There was one glioblastoma (the most malignant primary brain tumor), but this occurred in a patients who had previously undergone stereotactic radiosurgery (SRS) for vestibular schwannoma, which was thought to be the inciting event. Overall, the authors concluded that high-grade gliomas do not occur spontaneously in patients with NF2. Radiation is a known risk factor for high-grade glioma development, and should be taken into consideration when determining patient-specific therapies.

**b. Risk of Genetic Disease with Solitary Tumors**

To gauge the likelihood of an underlying genetic syndrome in patients with early schwannomas or meningiomas, Pathmanaban et al. (United Kingdom) studied children and young adults <25 years old who presented with a single schwannoma or meningioma and no known genetic disease. They sought to uncover the frequency of underlying tumor predisposition syndromes, such as NF2 or schwannomatosis. Using the database of a large, expert, academic NF2 and schwannomatosis clinic, they reviewed the charts and genetic testing of 42 patients with single meningiomas (median age 11 years) and 135 patients with single meningiomas (median age 18 years). In the meningioma group, 38% of patients were ultimately diagnosed with a mutation that predisposed them to tumor development, whereas 20% of the schwannoma group was diagnosed with a predisposing mutation. Next, the authors expanded their population by querying their database for any patient presenting with a single meningioma or schwannoma (even if they had a known underlying genetic disease). Of 63 patients who presented with a single meningioma, 54% had an underlying gene mutation associated with tumor development, which included 25 patients (40%) with NF2 and 9 patients (14%) with SMARCE1 mutations (which has been correlated with familial meningiomas in the absence of NF2). Interestingly, the group identified a
significantly higher likelihood of underlying genetic disease for single spinal meningiomas rather than cranial meningiomas. Of the 153 patients who presented with single schwannomas, 29% had an identifiable genetic mutation predisposing to tumor development; this risk was higher for spinal schwannomas (55%) than cranial schwannomas (18%). For those patients with cranial schwannomas, the risk of NF2 was 9% while the risk of LZTR1 mutation (which is associated with schwannomatosis) was 4%. Notably, NF2 was the more likely underlying genetic disease for patients presenting before 16 years old, and schwannomatosis was the more likely disease 16-24 years old. In summary, while meningiomas and schwannomas are common sporadic tumors in the general population, this study highlights that a significant proportion of patients <25 years old who present with apparently sporadic tumors may have underlying genetic predisposition. Such patients should be referred for evaluation and potential genetic testing in neurofibromatosis clinics.

c. Associating Genetics with NF2 Disease Severity

Halliday et al. developed an NF2 Genetic Severity Score – correlating genetic mutation with disease severity – and published a report validating its use in clinical and research settings. Their scoring system is broken into categories that include either presumed or verified mosaic disease (where an NF2 mutation is present in some, but not all, tissues), mild, moderate, and severe mutational types (which are specified in the paper, and relate to specific types and locations of mutations). While the authors list a large number of disease status indicators that correlate with the NF2 Genetic Severity Score, most notably they found significant correlations between mutation type and age at diagnosis, age at first NF2-associated treatment, presence of certain tumor types and locations, and hearing status. This study builds on previous work by many other author groups, highlighting the importance of specific NF2 gene changes in the prediction of disease outcome and severity. Still though, much remains to be learned about genotype-phenotype correlations. Even with scoring systems such as this one, clinicians are notoriously inaccurate at predicting specifics of an individual patient’s disease outcome or severity; patients should discuss these considerations with their NF2 physician.

5. Schwannomatosis Update

The Bottom Line: Laboratory-based research provided some long-sought answers on the differences between schwannomatosis and rhabdoid tumor predisposition, between sporadic and genetic disease-associated schwannomas, and has also developed an important new mouse model of schwannomatosis.

Schwannomatosis, the most recently described of the neurofibromatoses, remains both a diagnostic challenge and a genetic mystery. Researchers continue to search for molecular causes of schwannomatosis, and distinguishing features between schwannomatosis and NF2.

a. Mutational Timing Determines Tumor Syndrome Type

Blood (germline) mutations in the SMARCB1 gene are associated with two distinct diseases which do not overlap: some patients develop schwannomatosis, which leads to the development of non-malignant nerve sheath tumors and meningiomas, while other patients develop a completely different predisposition for malignant rhabdoid tumors. To date, little is understood about what differentiates these populations of patients, but Vitte et al. (United States) sought to tackle this question in the lab. Using various genetically engineered mice, the investigators determined that SMARCB1 mutations that occur very early in the development of a fetus (involving early neural crest cells) lead to rhabdoid tumors, while later mutations (involving Schwann cells) are prone to developing schwannomas when they co-occur with NF2 gene knockout. This knowledge of mutational timing is an important discovery toward
understanding causes (and potential treatments) of schwannomatosis. Even more importantly, through this work the authors created the first mouse model of schwannomatosis that carries the same underlying mutations found in patients, opening countless possibilities for study of disease progression and treatment considerations.

b. Distinguishing Sporadic and Schwannomatosis-Associated Schwannomas

Similar to the clinical question explored above by the work of Pathmanaban and colleagues, Caltabiano et al (Italy) sought to explore differences between sporadic and genetic predisposition-associated schwannomas. Here, the authors used SMARCB1 testing (by antibody staining) for this determination. The group pooled samples from a mix of 22 patients who were known to have schwannomatosis (including both SMARCB1- and LZTR1-mutant disease, either familial or non-familial), NF2, or solitary sporadic tumors. After a blinded review of SMARCB1 staining patterns, the authors determined normal (diffuse) staining in all patients with sporadic peripheral schwannomas. For patients with schwannomatosis (regardless of heredity or mutational status), all tumors stained with a mosaic pattern, with 10-70% of cells showing SMARCB1 expression. Among those patients with NF2, vestibular schwannomas stained with diffuse SMARCB1 expression, while peripheral schwannomas had mosaic expression. In summary, the authors concluded that differences in schwannoma SMARCB1 expression suggest differences in tumor development between patients with sporadic schwannomas and those with underlying schwannomatosis or NF2. Further, the authors suggest that the pattern of SMARCB1 expression in schwannomas may help distinguish between sporadic solitary tumors and those of patients with schwannomatosis or NF2. The total number of patients and tumors was quite small, though, and so expansion of this work will likely be necessary before utilizing this testing in clinical practice.

8. Communication with Medical Teams

The Bottom Line: New research highlights gaps in communication between care teams and patients and families, and suggests ways to improve the effectiveness of healthcare visits.

a. Health Literacy

Sometimes it feels that healthcare transpires in an entirely non-English language. Even when doctors explain things in lay terms, though, certain concepts or ideas may still be difficult to grasp. Accurately measuring patients’ understanding of healthcare ideas is a necessary step in improving patient-physician communication.

Merker et al. CDMRP, NIH (United States) used two validated tools to measure health literacy (“the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions”) in 86 patients with NF1, NF2, or schwannomatosis. Overall, the group found moderate health literacy scores across all patients, though various analyses showed patients with NF1, with learning disabilities, or with lower education did have lower health literacy scores. The authors suggest that evaluating individual patient health literacy using the tools in this study may provide valuable information and allow physicians to tailor health communication to maximize effectiveness.

*Disclosure – The author of this newsletter is also a co-author of the study by Merker et al.
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The Network Edge Archive

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