BPAN Warriors: A Rare Disease Community’s Search for Connection, Collaboration and a Cure

The Best of the Story ... a Q&A with Sarah Chisholm, one mothers’ resolve leads to a groundswell of support that becomes the BPAN Warriors.

Sarah Chisholm has three daughters, Ella, Emma, and Eva, with her husband, Robert. She was born in South Korea and adopted at the age of 5 with her brother. Sarah was subsequently raised in Bergenfield, NJ and attended the University of Pennsylvania. After a decade in Philadelphia, she transplanted to South Florida where she met and married Robert. Sarah currently owns and operates a small decorative hardware business, BCI Decorative Hardware, which has served a niche market of custom home builders in South Florida for the last decade. By the year’s end, Sarah hopes to dedicate her time and efforts to BPAN Warriors full time. She is a certified RYT200 Yoga Instructor and enjoys dancing, baking, gardening and crafting.
At the end of March 2017, her youngest daughter, Eva, now six, was diagnosed with a rare genetic condition called Beta-propeller Protein-associated Neuro Degeneration - BPAN - a devastating, life-limiting condition which affects approximately 500 people in the world (mostly girls). BPAN can cause a host of symptoms starting in infancy including cognitive and motor delays and Autism related behaviors. Many children do not acquire speech or have very limited speech. Additional symptoms include disordered sleep patterns (Eva has only slept through the night a few times since birth), complex seizure disorders and vision issues. The range of symptoms and the severity of the symptoms vary for each individual.

In late adolescence or early adulthood, Eva will experience a sharp and rapid cognitive decline accompanied by adult-onset movement disorders, including dystonia (painful muscles spasms) and Parkinsonism. The cruelty of the disease will eventually lead Eva to dementia and loss of life. At this time there is no treatment... and NO CURE.

Fortunately, Eva is very healthy, for the most part. She is a sweet, irresistible child. Anyone she meets eventually falls under her spell. Her deep brown eyes lure you in and it is all but impossible not to fall in love with her. Although she is non-verbal and has very limited means of communication, she somehow knows how to make others feel so very loved. She does suffer from a variety of seizures (which has landed her in the hospital for several multi-day stints), however they are for the most part under control through therapeutic interventions. Most recently, Eva (who is vision impaired) has been diagnosed with optic atrophy, which may eventually lead to complete loss of vision. Nevertheless, she is generally very healthy and happy and continues to make progress every day.

Sarah has dedicated this last year developing the foundation to support BPAN Warriors. It is currently the only U.S. based organization dedicated to advancing BPAN research. She leads a small team of staff and volunteers who work together in hopes of expediting scientific research that will advance therapeutics and accelerate a cure for BPAN.

We contacted Sarah to answer a few questions about BPAN as well as the organization she founded, BPAN Warriors.

Q [First question is to orient listeners, then move to content, etc] Can you please explain BPAN – symptoms and the consequences of the condition?

A Beta-propeller protein-associated neurodegeneration (BPAN) is an X-linked, monogenic, neurodegenerative disease, caused by mutations in the WDR45 gene. Although BPAN is a genetic condition, it is usually not inherited from a parent (see link to BPAN at http://nbiacure.org/). The condition presents with childhood developmental delay and seizures, shortened life expectancy due to complications from infection and progressive loss of neurological and muscle function. BPAN is part of a heterogeneous group of disorders known as neurodegeneration with brain iron accumulation (NBIA) that lead to progressive damage in the nervous system and a buildup of iron in the brain.

The WDR45 gene is responsible for encoding the WIPI4 protein, which has been implicated in autophagy and helps regulate key steps during autophagosome formation and elongation involved in the early stages of autophagy. Mutations identified in people with BPAN show impaired WIPI4 production leading to the loss of WIPI4 protein function. Loss of WIPI4 function results in impaired autophagy and makes cells less efficient at removing damaged cell structures and waste materials.

BPAN’s biphasic disease progression beginning in early infancy includes developmental delay and ataxia, intellectual delay with limited to no expressive language, early onset seizures which may present in infancy (infantile spasms and febrile seizures) as well as epileptic syndromes, including Lennox-Gestaut and West Syndrome, Rett-like symptoms including breath-holding, hand-wringing, bruxism when awake, and sleep abnormalities, automatism, perseveration and communication and social difficulties associated with Autism and ophthalmological and auditory deficits.

Patients experience slow motor and cognitive gains until late adolescence or early adulthood at which time, BPAN leads to progressive decline in ability and function which includes painful dystonia starting in the upper limbs, increasing cerebellar ataxia and spasticity, progressive parkinsonism (bradykinesia, rigidity, freezing of gait, and postural instability), and neurologic deterioration and loss of intellectual functioning that leads to a severe loss of cognitive and reasoning abilities (dementia).
Ultimately, BPAN leads to shortened life expectancy due to complications from loss of neurological and muscle function and from infection. At this time there are no treatments other than symptom management.

Tell us about BPAN Warriors – its function, how it came about, your role?

Established in 2018, BPAN Warriors is a 501(c)(3) organization whose mission is to actively support, facilitate and expedite therapeutic initiatives and scientific research that will enhance the quality of life for individuals living with BPAN. We mobilize and empower BPAN families worldwide, through access to community resources, information and most importantly, connection to our BPAN Warrior Tribe.

I think I can speak in behalf of all rare disease parents that not one of us has ever thought of leading the development of a research network prior to our child’s diagnosis. However, out of necessity and love, we have become the experts. In 2018, ten months after my daughter’s diagnosis, I redirected my early frustrations and launched the BPANWarriors.org website to provide a voice for our patient community along with much needed resources. Using my 20+years of experience in sales and new business development/marketing, I have since turned my focus towards making plans to secure resources and build an infrastructure to support patient-centered research.

Much of this last year has been invested in developing the infrastructure to support our fledgling non-profit, learning more about BPAN (the disease mechanism, the science and the existing research), identifying gaps in the overall research, and then diligently working to flush out a strategic plan to meet the needs of our growing community. My focus has been on how we can capitalize on the existing research within the Neurodegenerative space and what technologies or collaborations would help bypass existing inefficiencies or might serve to codify a strategy towards uncovering a therapeutic path.

Although the science may be complex, I remain undaunted. We have the ability to leverage new technologies, patient-centered data collection systems and ongoing data analytics and systems biology which would allow us to identify biomarkers, test new and existing drugs and potentially apply existing gene therapies to cure a relatively “simple,” monogenic disease.

I understand that diagnosis is an issue in general for rare conditions. Often children go years before a rare condition is correctly diagnosed, resulting in delays when possible treatments may have been started. Could you tell us about your journey in this regard (if you are willing)?

Discovered in 2004, WDR45/WIPI4 gene belongs to the WIPI protein family; this family of proteins plays a key role in autophagy, a cellular survival program that is compromised in neurodegeneration. The discovery in 2012 that mutations in WDR45/WIPI4 are causative for BPAN ended the diagnostic odyssey for some patients who had gone 15-30 years misdiagnosed or undiagnosed. Although an MRI may show a buildup of iron in the brain, iron accumulation may not occur until late in the disease. Even with clinical and MRI findings, genetic testing is the only way to confirm a diagnosis.

Access to whole exome sequencing (WES) and the addition of WDR45 to epilepsy genetic panels and mitochondrial panels has led to a dramatic increase in diagnosis and earlier diagnosis. Whereas two years ago, many patients were diagnosed upon entering regression/decline, many patients today are diagnosed upon onset of seizures, some as young as eight months.

Nevertheless, due the heterogeneous nature and wide range in severity of symptoms and symptom overlap among other diseases, patients may often go misdiagnosed (CP, A-Typical Rett Syndrome, Autism, Spastic Paraplegia and IDD are common diagnosis), or undiagnosed. With access to improved and cost effective genetic testing, early diagnosis is possible.

How can an early diagnosis be better implemented?

Truthfully, much has improved since 2012 when WDR45 was first discovered as causal for BPAN (and possibly other neurodegenerative conditions). WDR45 has since been added to multiple epilepsy panel, especially when patients are symptomatic of IDD and epilepsy. In addition, BPAN has been added to multiple mitochondrial panels as well as genetic testing screens for Rett Syndrome, Fragile X, Angelman Syndrome and other autism linked genes.

The addition of WDR45 to these genetic panels has had a direct impact in the number of recent diagnosis. In 2017, the number of confirmed BPAN cases was under 100 worldwide; today that number has been estimated by some at 500, although recent reports show that BPAN accounts for 40-45% of all NBIA conditions, which would place the number of patient diagnosis closer to 2000 worldwide. As a patient community, we see at minimum 2-3 diagnosis a week and sometimes see as many as 1-2 per day.

We could say better awareness of the disease and symptoms would provide earlier diagnosis, however, with the overlaps that BPAN shares with a multitude of other rare diseases and the broad range and severity of symptoms, the clinician burden would be monumental to know each disease. Rather, access to early genetic testing may prove to be the best route to improved diagnostics. Earlier diagnosis would
the lack of information and care guidelines that patients receive due to the lack of information and care guidelines that are currently available. Our goal is to provide better tools to support the medical community.

What treatments are currently available for this condition? Can you discuss long-term care options?

At this time, there are no treatments specifically for BPAN. Rather, treatment is limited to palliative care and support. Treatment for seizure management and pediatric epilepsies is an area which requires immediate attention. There are great challenges diagnostically and variability in treatment options and a still wider range in AED efficacy and side effects to be considered. Over the last two years there has been increased focus in the area of precision medicine in the area of rare disease and Developmental & Epileptic Encephalopathies (DEE). With many BPAN patients diagnosed with infantile spasms, LGS and West syndrome and other epileptic encephalopathies, seizure management has emerged as a critical area of concern for patient caregivers. Sleep dysregulation, chronic infections, and GI and endocrine issues are also areas where a consensus in patient care guidelines is inconsistent. This is where BPAN Warriors have had the benefit of gleanings from other rare disease communities with symptom overlap and currently works within a DEE consortium with evolving work groups to better understand available treatments for some of these common, shared symptoms across disease communities.

For some of our patients who experience muscle spasms or decreased mobility due to tightness of muscle or dystonia and Parkinson’s like symptoms, drugs such as Botax injections, Levodopa and Sinemet, are commonly administered within our community, as are a handful of psychotropic drugs which may be co-administered to support patient sleep and anxiety-related issues. With symptoms that overlap with many known diseases, currently the treatment path does not differ much from the available symptom management available to the wider movement disorders community, as well as those with Parkinson’s or Alzheimer’s Disease.

Although there are over 400 WDR45 related published case studies, currently no BPAN specific research network exists. While there are no clinical trials specifically for the treatment of BPAN, there is a clinical trial for Deferiprone, an iron chelation therapy, which is currently active for another related NBIA condition. Our patient community could potentially participate, however case studies which included BPAN patients indicate that the efficacy of Deferiprone is questionable and not without side effects. Whether the benefit would potentially outweigh the risk would need to be further explored as it is still a matter of debate as to whether iron accumulation is a primary cause or secondary event in reduced autophagy, mitochondrial abnormalities, oxidative stress, and diminished lysosomal function.

An effective BPAN treatment would need to target the “root” cause. Use of autophagy regulators to induce autophagy may provide a therapeutic target, as may attempting to repair the defective autophagic machinery, by promoting autophagosome elongation and closure, thus preventing protein aggregation and limiting oxidative damage. Also, exploring how iron dysregulation, the metabolism of iron, and more specifically how heme/non-heme iron and ferritin are stored, absorbed, and made available on a cellular level may be of great import for our disease. We still have many avenues to explore for potential treatment given the centrality of iron homeostasis and autophagy in basic cellular function.

What can you tell us about treatments currently in development - e.g., standard small-molecule drugs? gene therapies? cell-based treatments?

Knowing that autophagy has emerged to play such a critical role in disease research, we believe that we must expand our research scope to include other neurodegenerative conditions, autoimmune conditions and other childhood epilepsies and encephalopathies such as Rett Syndrome and CDKL5. Symptomatically, our disease has incredible overlaps with other neurodegenerative diseases including Parkinson’s and Alzheimer’s and other rare diseases that have multiple treatments in their pipeline. There may also be overlaps in cardiomyopathies, glucose metabolism, lysosomal storage disorders, autoimmune conditions and innate immunity and immunological deficiencies.

WIP1, the protein encoded by the WDR45 gene, is expressed throughout the body and autophagy, mitophagy and iron regulation play a pivotal role in numerous disease pathologies, including cancer. WIP1 mutations in BPAN patients provided the first direct evidence that autophagy malfunction may be a significant contributing factor (if not causative) of neurodegeneration in humans; WIP4 mutations in BPAN patients lead to the accumulation of early autophagosomal membranes and improper autophagic degradation. Emerging research has now identified WDR45 as one of the top 10 new genes for Parkinson’s disease by IDLP1 and in a large-scale genome analyses, three mutant WIP1 and WIP4 variants were found in analyses of lung cancer.

With the increased interest in autophagy related research across disease communities, we know that the opportunities are abundant to apply existing research to our disease. CDKL5, Rett Syndrome and Angleman Syndrome provide some interesting opportunities for treatment therapeutics in both gene therapy and small molecule drugs. Currently several BPAN researchers are in the early phases of testing existing FDA approved drugs in patient-derived neurons, with the hopes that they may be re-purposed for the benefit of our community.

The greatest obstacle is not so much the breadth and lack of potential disease modifying pharmaceuticals but rather applying the existing science and data to provide streamlined targets to expedite the therapeutic timeline. With the heightened and broadening interest in rare diseases and opportunities afforded our community through the Orphan Disease Act, the marketing exclusivity and tax incentives afforded to researchers and industry alike, we now have an environment that is rich with opportunity to accelerate drug development. Pharma is also interested in novel targets and compounds to test for alternate indications for other therapeutic uses.

Beyond chelation therapies and autophagy regulators, there may potentially be an option to develop a nano-protein which can cross the blood brain barrier. In recent studies, overexpressing WDR45 wild-type protein in patient-derived neurons restored LC3-II levels in patient cells, which would indicate autophagy induction. In effect, overexpressing the WIP14 protein may potentially repair the autophagy defect in BPAN patients.

Precision medicine tools should (or should have already) have impact in diagnosing the conditions - e.g., bringing down the cost of sequencing, etc to make diagnosis more affordable. How do you foresee precision medicine accelerating treatments for BPAN?

The multiple roles of autophagy in...
1) infectious diseases (bacterial and viral); 2) tumor suppression/progression; 3) brain development/neurodegeneration; 4) the immune system; and, 5) autoimmune diseases, as well as its other roles, have been widely researched. These studies have elucidated the implications of autophagy in cardiovascular diseases, iron homeostasis, obesity, diabetes, and diseases caused by defects in autophagy genes.

Platforms such as Genomenon and Mastermind provide patient communities, researchers, and industry the ability to rapidly assimilate information. Through the use of increasingly complex and accurate mathematical models and algorithms, large amounts of information, potentially across disease communities, can now be collected, analyzed, and distilled into usable datasets. This process, which in the past may have taken months if not years to manually input, upload, and analyze, is now completed within minutes and hours, depending on the complexity of the data, and made available to the end-user in a user-friendly, yet robust, scalable, online platform. The emerging field of bioinformatics and systems biology coupled with the rapid scientific discoveries, may allow genomic data to identify potential bio-markers and targets for drug therapies.

Despite all these advances, patient engagement and collaboration among our research community is imperative to efficiently collect patient information, patient reported outcomes, biological samples, natural histories, etc. In this sense, the patients themselves are still at the forefront of championing research, not just with passion and vision, and of course funding, but with the ability to collectively provide and make accessible essential data so that these tools that can drive precision medicine forward may be utilized.

How do you see the research – early stage through to clinical – providing benefit to those with BPAN?

Early on, we recognized the need for a collaborative network of scientists, researchers, patients, and other stakeholders (those in the pharmaceutical and biotech industries). A research network is essential in helping us understand and prioritize the most relevant and promising research approaches for this disease. Currently there are no FDA approved treatments for BPAN, no clinical trials underway, and no labs investigating cutting edge approaches, such as gene therapy, for BPAN. As an organization whose aim is to fund the most promising research, it is essential that we have consensus on what research questions are most important to answer in order to have the greatest impact for patients.

With global partner Genomenon, our organization has been able to rapidly assess the research landscape and identify the key scientific talent in BPAN and related research, we can now launch our tiered strategic plan to accelerate BPAN treatment options. With our online data collection partner Backpack Health, we will now begin the process of collecting vital patient information from the US and abroad. This will coincide with the development of a centralized bio-repository to be housed at the Coriell Institute, allowing for uniform screening, karyotyping and cataloguing of patient bio-samples and more importantly, greater access to research and industry partners. Our plan is to leverage these partnerships to promote BPAN Warriors to existing and newly diagnosed families around the world. Participation from families is vital to the success of these initiatives.

In addition, we are now establishing parallel paths of research in both gene therapy and potential therapeutics that may induce autophagy. One of our most pressing goals is to evaluate known BPAN isoforms and identify/validate which isoform(s) is the best candidate to deliver via AAV gene therapy. Our current understanding is that there are multiple WDR45 isoforms that currently exist and therefore we will need to target the isoform(s) with the highest protein expression or those that have the highest impact in neural/cellular function. The study of isoforms and what we learn over the next year will potentially shape our short term and long-term therapeutic objectives. In short, the isoform study will dictate if gene therapy is even a viable option.

One more question (and let me know if this is okay): What advice would you give to a parent or parents whose child has been diagnosed with BPAN?

I try to steer clear of giving advice and prefer to share my experience. As a parent who is now 2.5 years into this BPAN journey, I recognize that nothing about the disease is “simple.”

The science, the symptom management, daily patient care, navigation through insurance and IEP’s; the list is endless. What holds true today and was true when my daughter Eva was diagnosed at age four is that I am not alone. Oftentimes, I do struggle with the weight of this disease, and the feelings can be overwhelming. These are the times that I have to remember that I am not alone. There are others who are going through the same exact journey. Our circumstances and background may differ, our children’s capabilities may be varied, however in the end, we are parents who are all doing the best that we can for our children. Not everyone is going to dive into research, or start fundraising; many may be overcome by shock, anger and grief. Still others may have to contend with the real-life implications of caring for a child with very complex medical needs.

Whatever our stories are, we are connected. I did (and still do) experience a range of feelings. I can honestly say, however, that since I was able to connect with others, some of the sense of “aloneness” dissipated. That is not to say it has all vanished, rather, the pain has dulled and has been replaced by a new sense of purpose.

This does not in any way diminish the devastation of a diagnosis and the tremendous obstacles that so many families encounter every day. What it does for me today is provide me with the impetus to move forward, persist, ask questions and recognize that as humans, we can oftentimes achieve the seemingly impossible.

Every rare disease therapy that I have read about has been brought to trial, greatly in part due to the herculean efforts and tenacity of a parent or set of parents who did not know (or accept) that what they were trying to achieve was impossible. Today, I credit those families for inspiring me to challenge my limitations and the limitations of science, medical institutions and even our very own disease community. The path is not easy however I can look at my daughter every day and say that I am doing my very best to ensure that she has every possible opportunity for quality of life.

Ultimately, I have a tremendous amount of hope. I do believe that there is a potential for a treatment for BPAN and a cure IS possible. Some would say this is a fool’s folly; I would rather believe it is based in the merits of the science.

References