

## An Ultra-rare Disease? Where Do We Go from Here?

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### Abstract

When people are diagnosed with rare, incurable disorders, they and their families suffer both from the disease itself and from the lack of information and resources available. They become acutely aware that research can only be conducted when it is funded. This article presents our experiences following the diagnosis of our daughter with chorea-acanthocytosis, and describes how we established a not-for-profit organization to fund and facilitate research into this rare disease. Personal relationships with clinicians and scientists, and with friends who were willing to help, have played an essential part in moving the field of neuroacanthocytosis research forward.

**Keywords:** Patient advocacy, neuroacanthocytosis, rare disease

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### Introduction

At the age of 24 years, our articulate daughter began to mumble. Over the next few months occasional, hardly perceptible, involuntary arm movements developed into sudden, uncontrollable flailing. It slowly became clear that our daughter was not merely experiencing delayed adolescent awkwardness. A long trail of medical consultations wound from primary care to in-hospital observation, and through to the top neurological specialists. Countless tests and biopsies excluded many possible diagnoses. Finally, at a Grand Rounds session, a geneticist asked if our daughter's blood had been checked for acanthocytes. Acanthocytes were found, and a few days later our daughter was discharged with a diagnosis of neuroacanthocytosis (NA).<sup>1</sup>

Searching the web, we found that only a few clinical observations<sup>2</sup> had been published since Levine et al. and Critchley et al. first identified the condition in 1968.<sup>3,4</sup> This was not surprising, as the frequency is estimated to be 1 in 10 million.

Reluctantly, our daughter settled into the safe environment of her childhood home in London and received excellent care from the National Health Service. Through sheer chance, we discovered that research on NA had recently begun at the Wellcome Trust Centre for Human Genetics at the University of Oxford,<sup>5</sup> and that a clinical study was about to be carried out at the US National Institute of

Neurological Disorders and Stroke by Adrian Danek, MD, who was undertaking a fellowship there.

What could we, as parents, do? There was no patients' organization concerned with the disease, but it was evident that a number of clinicians and cell biologists were interested. The interest of these professionals was our motivation. While there was no hope that we could contribute to the science and, we thought, little chance that we could raise money, there were some small things we could do. The first step was to translate into English Dr. Danek's application (in German) for funding for a proposed first symposium on NA. The closing of US airports following the events of September 11, 2001, led to an unexpected visit from American friends who stayed with us while waiting to return to New York. When they heard of the proposed symposium they offered to help make it happen, and we were launched.

The infectious enthusiasm of the professionals at this first symposium in Germany in 2002 and our own hope of doing something to help created a "movement" that needed a name: "Advocacy for Neuroacanthocytosis Patients" was born.<sup>a</sup> Raising

<sup>a</sup>Advocacy for Neuroacanthocytosis Patients was incorporated and registered as a charity by the Charity Commission of England and Wales in 2009. Before this, the charity "John Grooms" handled the Advocacy's finances.

\$5,000 to fund the publication of a book, *Neuroacanthocytosis Syndromes*,<sup>6</sup> which came out of the first symposium, became our first attempt to ask friends and neighbors for support. Their response was greater than we had ever imagined and set us on the road to the next symposium, another book, and providing modest research grants.

### What Can We Do? Roles for Patient Advocacy Groups

#### Supporting patients and their families

At the heart of our movement are people isolated by an all-consuming chronic dependency. The clinicians we met initially put a few affected families in contact with us and our reach slowly widened, but even after 11 years increased awareness is needed to reach all who might benefit from mutual support. Most of our contacts still begin with clinicians suggesting the Advocacy to those patients who are interested in talking with others who share their position. The internet and e-mail are invaluable channels for families who need information and, above all, human contact with others who understand and share their anxieties, concerns, and hopes. Our active approach to this “market” came from a pioneering publicist friend, Sheila Averbuch,<sup>b</sup> who generously offered to create *NA News*, an e-newsletter reporting on matters of interest to patients, clinicians, and researchers (available at [www.naadvocracy.org](http://www.naadvocracy.org)). Circulation has grown to 1,700 subscribers around the globe. Now in its 20th edition, *NA News* is available in five European languages and the search is on for Japanese and Urdu translators. Our website was created by a friend and was recently upgraded and expanded with the help of a professional consultant. A dedicated section of the website allows patients to write about their experiences with NA and exchange correspondence in a safe, monitored environment.<sup>7</sup> Translations into five European languages are also available. These translations are provided by the RareConnect service of the National Organization for Rare Diseases and EURORDIS, the European rare disease advocacy group. In addition, many of the language obstacles are overcome with French-, German-, Portuguese-, and Spanish-speaking “patient advocates,” who respond to e-mails from patients and families and support translation of the newsletter.

Diagnostic support and personal contacts have brought to light many new patients with NA, increasing the estimated number of people with this condition from 500 to 1,000 worldwide (A. Danek, personal communication).

#### Providing resources for clinicians

Even the most experienced neurologists in world centers of excellence are unlikely to see more than a few NA patients over their entire careers. Thus, a major responsibility for our patient advocacy group is to support opportunities for professionals to learn about NA and provide help with diagnosis, clinical experience, and patient support.

<sup>b</sup> Sheila McDonald Averbuch is a Harvard and Stanford-trained journalist who, with her husband, Ralph, created ENNclick, a content service focussed on the use of social media.

Dedicated medical professionals are vital contributors to this education initiative. One role of the Advocacy is to support symposia that are partly devoted to the clinical aspects of NA. Such meetings have been held in Munich, Montreal, Kyoto, London, Bethesda (MD, USA) and Ede. The publication of two books and several journal review articles based on contributions from speakers at our symposia provide an academic resource.<sup>6,8</sup> This resource is brought to life when “our” professionals are invited to speak at meetings of neurologists who are especially concerned with Huntington’s and Parkinson’s diseases. The book *The Differential Diagnosis of Chorea*,<sup>9</sup> edited by our colleague Ruth H. Walker, provides a framework for the neurologist observing undiagnosed chorea.

A free diagnostic service is offered by Ludwig-Maximilians Universität in Munich, with support from the Advocacy.<sup>10</sup> The test uses an antibody against VPS13A (vacuolar protein sorting 13 homolog A; also known as chorein), identified by researchers from the Wellcome Trust Centre for Human Genetics.<sup>11</sup> Absence of VPS13A indicates chorea-acanthocytosis (ChAc). If the protein is present then colleagues at University Hospital, Zurich, can determine if the Kx antibody is missing, indicating a diagnosis of McLeod syndrome (MLS).<sup>12</sup>

To facilitate clinical research and potentially collect pathologic samples, we have supported Ludwig-Maximilians Universität in collecting uniform, descriptive reports in a patient registry, hosted by the European Huntington’s Disease Network platform.<sup>c</sup> The VPS13A Western blot diagnostic service was planned to be a source of new entries into the Patient Registry, offered free of charge with the request that the requesting physician enter the patient’s information into the anonymized database.<sup>13</sup>

Together with clinicians, the Advocacy encourages patients and their families to consider *post-mortem* tissue donation for research. When necessary, the Advocacy funds autopsies or transportation of samples to the tissue bank.

#### Basic scientific research

Prior to the first NA symposium in 2002, fundamental genetic studies had linked MLS to the causative *XK* gene<sup>14</sup> and Levine–Critchley disease, renamed ChAc, to VPS13A. These studies were performed at the Wellcome Trust Centre for Human Genetics, and their findings were soon independently confirmed by researchers at Kagoshima University.<sup>15</sup>

ChAc and MLS are both associated with degeneration of the basal ganglia. In addition to the similar movement disorders seen in both, they share two further common characteristics: 1) acanthocytosis (thorn-like membranes of red blood cells); and 2) absence of the expression of specific proteins (VPS13A for ChAc and Kx for MLS).

An initiative to study acanthocytes for clues regarding the pathway to neurodegeneration was proposed by Ruth Walker and Giel Bosman

<sup>c</sup>The European Huntington’s Disease Network and the CHDI Foundation are exemplary organizations pursuing the welfare of patients with Huntington’s disease and research focussed on therapies for Huntington’s disease. We are grateful to Professor Bernard Landwehrmeyer for his support of patients with NA.

in 2003. Starting with a small grant of \$10,000, this project continues with direct grants from the Advocacy and substantial grants from the E-RARE program.<sup>d</sup>

In 2006, a commitment of \$250,000 from a concerned donor provided the Advocacy with the resources for a planned research program. We learned a powerful lesson regarding the need for business-like management of grants following the funding of a project for a mouse model of ChAc that went unfulfilled. Thus, we set about looking to create an independent, outward-looking process that could objectively analyze grant applications. We needed experts in the basic cell biology of neurodegeneration as it related to the characteristics of NA diseases. Fortunately, introductions from another well-connected friend led us to form an independent and expert scientific panel.

In 2007, we issued our first call for research proposals. The application format was contributed by the Huntington's Disease Society of America and, with permission, we adopted the "Conditions on which a grant is awarded" of the Wellcome Trust. An important added condition was the requirement for a short twice-yearly progress report, suitable for lay people, to be published in *NA News*.

One successful application was for a grant to study the significance of the loss of VPS13A expression in ChAc, which grew out of the 2008 symposium in London and Oxford. The aims of the study included:

- Identifying the activity of homolog proteins in a yeast model.
- Creating and studying induced pluripotent stem cell neurons from ChAc patients, in search of the cause of and eventual therapy for NA diseases.
- Developing specific antibodies against VPS13A. These antibodies are essential for visualizing VPS13A in cells and tissue extractions, and to facilitate studies of cell biology and animal models.

To date, the Advocacy has invested \$544,000 in six research projects. This seed money has stimulated collaboration and interest, culminating in the creation of the European Multidisciplinary Initiative on Neuroacanthocytosis (EMINA), which in 2009 won a grant under the European Union's E-RARE program. In 2012 a second grant, for EMINA II, was successfully funded, and is supporting expanded studies of acanthocytes, molecular pathways in ChAc neurons generated from induced pluripotent stem cells from patients and controls, characterization of animal models of ChAc, and dissecting biochemical changes to ChAc neuronal networks.

These grants have added up to \$1,756,000 in research funding, and other recipients of Advocacy grants have been encouraged to apply for further funding from the National Institutes of Health.

### **Further roles and opportunities for our contributions**

Our success in recruiting growing numbers of scientists dedicated to the understanding of NA has brought with it the challenge of facilitating and building collaboration between geographically diverse research

efforts. Different teams will invariably observe different phenomena, and the Advocacy seeks to encourage and support the collegial spirit that has been a hallmark of the NA movement over the past 15 years.

Working with our professional colleagues, the Advocacy now aims to expand interest in the pathological pathway of degeneration of the basal ganglia, for example by finding new cell biology researchers to deepen the investigations into autophagy. In addition, the Advocacy is preparing for the time when understandings won by academic scientists can form the basis of collaboration with pharmaceutical and biotechnology companies in developing potentially therapeutic molecules, leading to trials and ultimately a therapy. Friends have introduced us to companies such as GlaxoSmithKline, Novartis, Boehringer Ingelheim, and Alexion. In addition to potential future collaborations on therapies, some of these companies have also supported our educational role. As academic research leads to a greater understanding of the pathologic processes involved in NA, collaborations with industry will make an important contribution to our ultimate goal of finding a cure.

Such a rare and dispersed disease presents practical challenges to research. For example, there are only a few tissue donors in any one country. Supplying tissue samples across borders is hampered by a lack of contacts and by national regulations regarding the use of human tissue for research. These are practical problems that support from the Advocacy can overcome. The Advocacy should continue to play a role in coordinating the supply of blood samples and patient information for research.

Another important role of the Advocacy, providing a conduit between patients and its professional partners, is that of supporting pharmacovigilance. Patient reports of both beneficial and harmful drug reactions will be encouraged and passed to the appropriate authorities.

The internet and e-mail have been crucial assets in supporting the widely spread patient group and developing the international research effort. While e-mail is convenient for most of the older generations, it may be replaced by other forms of social media, which resemble sensitive ears listening in on conversations and deciding which to follow. Many people do not regularly review either websites or patient-message exchanges such as RareConnect. Learning to use wider social media for the benefit of patients, patients' families, and professionals is a new challenge.

The progress made in the field of NA since 2001 has only been possible because of the generosity of donors and the voluntary contributions of medical professionals, families and friends of the Advocacy, and a myriad of volunteers. Important challenges include finding ways of continuing with this and identifying new leaders as the inevitable passing of leadership occurs.

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