I, Rebecca Sisson, hereby submit this original work as part of the requirements for the degree of Master of Science in Genetic Counseling.

It is entitled:
Assessing and Addressing Family Members' Attitudes and Perceptions of Acute Necrotizing Encephalopathy

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This work and its defense approved by:

Committee chair: Derek Neilson, MD
Committee member: Cynthia Prows,
Committee member: Lisa Martin, PhD
Assessing and Addressing Family Member’s Attitudes and Perceptions of Acute Necrotizing Encephalopathy

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Abstract

Acute necrotizing encephalopathy (ANE) causes lethargy, seizures and coma in children who are otherwise healthy. The condition requires an infectious trigger and has a genetic component as well. Children presenting with ANE start with typical childhood infections and develop flu-like symptoms. Instead of recovering, the children become increasingly lethargic. The symptoms usually lead to seizures and coma within 1 to 3 days. The outcomes of ANE episodes vary but can be devastating; from full recovery, to severe intellectual impairment, to death. Patients are spread all over the world, so there is little opportunity for families to communicate, and little information about ANE is publicly available. The goal of this study was to document the need for an ANE support network, and determine what families want most from a support network. Participants for this study were relatives of participants enrolled in a previous study about the genetics of ANE. An investigator developed, online questionnaire was first sent to physicians of patients who have ANE and then forwarded to families. We received 25 completed questionnaires out of 86 eligible families. Overall, 92% (23/25) of participants reported being interested in an online support network and anticipate using a network at least monthly (75%, 18/25). Participants ranked their interest in information about ANE and ANE research more highly than communication and emotional support. Most participants reported high levels of worry for their children and other family members. Reported levels of worry were significantly higher after experiencing an ANE episode. Worry was ranked on a scale of 1-10 with 10 being the highest level of worry. Participants were most worried about ANE during the winter/flu season (median response=9 (5.5-10)) and when a member of their family has a cold or fever (median response=10 (8.25-10)). Families reported that they have changed their lives and plans for the future after experiencing an ANE episode (median responses were 10 (8-10) and 9.5 (5.5-10)). Based on the impact that ANE has on the lives of families, their level of worry and the high level of interest in an ANE support network, this study shows that this type of network would be very useful for families. However, their preferences indicate that information provided through an online resource would be more important than the social aspect.
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Introduction

Overview of ANE

Typically when children acquire a flu-like infection, they are more tired than usual, develop a fever, and completely recover after several days. However, a small subset of children will progress into a much more serious illness. One to three days after the infection’s first symptoms they begin to demonstrate a progressive loss of consciousness, eventually becoming comatose. Seizures and neurologic disorders appear in approximately half of these children. If an MRI of the brain reveals bilateral lesions on the thalami, brainstem or cerebellum, this confirms a diagnosis of acute necrotizing encephalopathy (ANE) (Neilson, 2010). The cause of ANE is unknown for most cases, but in some, a contributing factor is an inherited predisposition. The most common inheritance is autosomal dominant and this makes for an unusual genetic disorder in that the disease state requires an infectious trigger to become manifest. The outcome of ANE episodes vary over a broad spectrum. About 60% of patients have a full recovery, about 15% have severe neurological impairment, and about 25% die after an episode. Recurrent episodes are rare, but tend to have worse outcomes than the first episode (Neilson et al, 2003). There is no cure for ANE and current treatments have limited effects. Some research has shown that corticosteroid treatment within 24 hours of the onset of an episode is associated with a better outcome (Okumura et al, 2008).

Prevention of ANE through vaccination

In half of the ANE cases in which a virus is identifiable, influenza A is the causative agent. However, the effect that the influenza vaccine has on ANE patients is not well known. The vaccine is probably protective against influenza infection and subsequent ANE episode, but parents are often afraid that it could trigger an episode (personal communication, Derek Neilson, 2011). One study in Japan looked at the incidence of febrile-related encephalopathies before and after a period of mass influenza vaccination. The incidence of encephalopathies increased when mass influenza vaccination ended. Although ANE was not directly studied, these results suggest a protective, rather than causative, role of the influenza vaccine in febrile-related encephalopathies (Ono et al, 2003).
Genetics

Initially, it was believed that the majority of cases of ANE were sporadic. This belief suggested that families did not need to worry about recurrent episodes or other family members. However, some families have been shown to demonstrate an autosomal dominant form of the disease, and there is a known genetic predisposition to developing ANE. This predisposition can be inherited through mutations in the \textit{RANBP2} gene (Neilson et al, 2009). Because the disease shows incomplete penetrance, a \textit{RANBP2} mutation is associated with a 40\% chance of developing ANE with a febrile infection (Neilson, 2010). This can result in increased anxiety because, in some cases, the disease appears to “skip generations” and may occur unexpectedly in a family branch previously thought to be “safe.” In at least four families a \textit{RANBP2} mutation was shown to segregate silently for one to two generations before becoming manifest again (Neilson, 2010). The mutation has also been seen in \textit{de novo} cases with no family history, and there are sporadic cases of ANE with no identifiable \textit{RANBP2} mutation. Recurrent ANE episodes seem to be more indicative of a \textit{RANBP2} mutation than family history (unpublished data, Derek Neilson).

Development & Interest in Online Support Groups

ANE affects children who are otherwise healthy, and its episodes are unpredictable. ANE episodes leave families feeling uncertain about their child’s future and the risk to other family members. Parents often request a resource for support and information (personal communication, Derek Neilson). Because ANE patients are spread across several different countries, it is nearly impossible to develop an in- person support network for this disease. Due to the rareness of this condition, an online support network could provide access for larger number of families than in-person meetings.

Through online support networks, patients can contact each other across large geographical distances, they can choose to remain anonymous, and they have 24 hour access to the network (Bartlett and Coulson, 2011; Cawdron and Issenman, 2002; Hoybye et al, 2005 & Wright and Bell, 2003). Previous research with other patient groups suggests a large interest in use of Internet resources for support. Studies have shown that most participants used online support networks for helping others,
sharing information, sharing their personal stories and social support (Bartlett and Coulson, 2011, and Cawdron and Issenman, 2005). Participants also reported that they gained feelings of enhanced social well being and they felt better informed after using an online support group (Bartlett and Coulson, 2010).

Although ANE is a very rare condition, its impact on families can be devastating. The main goal of this study was to document the need for an online ANE support network and to assess that impact that ANE causes on the lives of its patients and their families. Families were asked to describe the features of a support network that would be most important to them. Family’s level of worry and the changes they have made to their daily lives were also measured to determine other needs that should be addressed in a support network. A subset of questions asked specifically about vaccination and schooling choices. Parents often voice concerns about the safety of vaccinations, and also how to protect their children during the flu season (personal communication, Derek Neilson). For example, one way parents have tried to protect their children from developing an influenza infection is to take them out of school during the flu season. These questions were asked in order to better characterize the decisions that parents are making, and how much information needs to be provided on these topics. Participants were also asked if they had a known RANBP2 mutation. Because there is an increased recurrence risk associated with familial ANE, we wanted to determine if families who have known genetic mutations require different information and support than families who do not have a known mutation. This information could be used to further tailor support network needs.

Methods:

Study Population

Participants for this study were patients or relatives of patients who were previously enrolled in the study, Genetics of ANE (Principal Investigator: Derek Neilson, IRB# 2008-1307). Exclusion criteria included relatives of the patient who were under the age of 18, people who were not family members of a patient who has ANE, or people who could not read English. The 86 families enrolled in the Genetics of ANE study were our available population.
Study Recruitment:

A small number of patients who have had a clinical relationship with Derek Neilson, MD in the past and for whom he already had contact information were contacted directly. These patients were sent a letter electronically via email, explaining the purpose of the study, why they were contacted, and the link to the questionnaire.

When contact information was not available, the physicians who originally referred participants to the Genetics of ANE study were contacted first. The physicians received the letter and the link to the questionnaire electronically. Physicians were asked to contact their patients who have ANE, notify them about the study, and forward the letter and link to the questionnaire. Patients were informed that by reading and completing the study questionnaire they were giving their consent to participate in the study.

Due to a small sample size and low response rate, physicians and potential participants were re-contacted 6 weeks after the original questionnaire was sent. This was done electronically using the same letter and questionnaire. One month after re-contacting physicians and patients, a reminder email was sent encouraging patients to participate in the study and forward the questionnaire to their family members.

Online Survey:

Data was collected using an investigator developed, online questionnaire posted on the website, surveymonkey.com. The questionnaire was tested for readability by the members of the research advisory committee (RAC) and committee peers.

Participants were automatically diverted to a subset of questions for the entire questionnaire depending on whether they were affected with ANE themselves, if they had a child with ANE, if they were the primary health care decision maker for their child, or if they had another family member who had ANE. The questionnaire addressed what families want and expect from a support network for ANE, perceived levels of worry about ANE, and how families have changed their lives in response to ANE. For this study worry was defined as “feelings of uneasiness or uncertainty regarding a family member’s ANE
diagnosis.” Most questions included in the questionnaire were quantitative, although there were options for participants to elaborate on their answer choices with descriptive information. Specific support network interests, perceived levels of worry, and the amount that participants have changed their lives in response to ANE were all ranked from 1-10. Two specific lifestyle changes that were included in the questionnaire were vaccination and schooling choices because these are concerns frequently voiced by parents (personal communication, Derek Neilson). Only the parent who was the main medical care provider for their child answered these questions to prevent duplicate answers from one family.

Data Analysis:

Data from SurveyMonkey® was downloaded into a standard file format. Data was then imported into JMP (Sas Institute, Carey NC).

Summary descriptive statistics (frequencies or means +/- standard deviations) on cohort characteristics (age, gender, country, education, age of ANE diagnosis, ANE associated mutation status, and participants relationship to patient who has had ANE) were calculated. Because data were not normally distributed, results for responses using Likert scales were reported as medians with the interquartile range. Additionally, we visually reviewed and reported participant responses for other important features of a support network and long-term complications due to ANE. Comparisons for responses using Likert scales were done using paired non-parametric Wilcoxon signed rank tests. Comparisons based on mutation status were made using non-parametric Wilcoxon tests.

Results:

Demographic data:

At the close of the survey we received 36 responses. Eleven responses could not be used for data analysis because the participants were under the age of 18 (n=4) or did not report their ages (n=7).
Of the 25 participants, most were between the ages of 28 and 47. Males and females were represented equally and most participants had at least a college education. Participants were from 13 different countries, although most were from the United States (Table 1).

The majority (85.0%) of participants' families had participated in genetic testing for ANE, although more than half (56.0%) did not have an identifiable mutation in the RANBP2 gene (Table 2). Sixty-five percent of participants responded to the survey because their child had an ANE episode. Of the described ANE cases, (65.0%) had 2 or fewer ANE episodes and survived for an average of 3.9 years with long-term effects (Table 3). Long term effects included behavioral, vision, and cognitive problems as well as loss of gross and fine motor skills.

**Interest in an Online Support Network:**

The main goal of this study was to determine if families would be interested in an online ANE support network, and what they would like to achieve using a network. An overwhelming majority of participants reported that they would be interested in an online support network for ANE (92.0%), and 75.0% reported that they would access the network at least monthly. The level of interest in six common features of support networks was evaluated and responses were included in Figure 1. However, there seemed to be a larger interest in information and research than communication and emotional support. Emotional support received the lowest median ranking and was significantly less important to participants than information about ANE (p=0.0001, S=52.5), information about ANE research (p=0.0004, S=56.0), fundraising for ANE research (p=0.0009, S= 59.0), and communication with other ANE families (p=0.0181, S= -29.5). Level of interest in each of the six features did not seem to vary based on mutation status (see Table 4 for p values and test statistics).

Regarding information that should be included in a support network, participants were highly interested in information about symptoms, prognosis, treatment and management, genetic testing and inheritance, and current ANE research (Table 5). Participants ranked the highest level of interest in communicating via an online message board (median response = 8.5 (5.5-10)) and slightly more than half
believed that medical professionals and families affected by ANE should have access to the support network (58.3%). Other interests that participants reported included: a directory of medical professionals who specialize in ANE, a map of where families are located, information about other conditions associated with ANE, and that comments made on a message board remain anonymous.

**Worry about ANE and further defining support network needs:**

In order to further define support network needs, frequency and level of worry were quantified and participants were asked to rank a list of potential sources of worry. Participants were given the option to continue the survey or stop at this point. Of the 21 participants who chose to continue the survey, most reported high levels of worry regarding ANE (median response= 9 (6.5-10)). Because there was no control group for this study, we asked about levels of worry before and after ANE in order to assess how much worry is caused by ANE. Participants reported significantly higher levels of worry about seven different sources after experiencing ANE (Table 6). Participants reported the highest levels of worry during winter/flu season (median response = 9 (5.5-10)) and when their family member has a cold or fever (median response = 10 (8.25-10)). The levels of worry in these two categories were highest both before and after ANE, but did appear to increase after an ANE diagnosis in the family (see Figure 3 and Table 6).

Most participants reported that they worry at least weekly about their family member having another ANE episode (63.2%), other family members having an ANE episode (70.0%), and their other children or future children developing ANE (55.0%). Most participants (89.5%) reported that they worried about their family’s health monthly or less before their family member developed ANE. The frequency of participants’ worry did not appear to vary based on mutation status (Table 7).

Although the results were not statistically significant, participants whose family member did not survive an ANE episode tended to worry more than those whose family member did survive. When asked how often they worry about other family members developing ANE, 75.0% of participants whose family member did not survive worry at least weekly, versus 46.7% of those whose family member did survive.
All participants whose family member did not survive worry that their children or future children will develop ANE, versus 58.3% of those whose family member did survive (Figure 4).

Although not statistically significant, participants whose family member fully recovered from their ANE episode seem to worry more than those whose family member has long term effects from an ANE episode. Of participants whose family member fully recovered from an ANE episode, 100% worry that their family member will have another episode, that their other or future children will develop ANE and that other family members will develop ANE. Of participants whose family members have long term effects from ANE, 58.3% worry that their family member will have another episode, 50.0% worry that their other or future children will develop ANE, and 58.3% worry that their other family members will develop ANE.

**Lifestyle changes in response to ANE:**

Members of other disease-specific support groups often communicate with each other in order to gain information about caring for their child and coping with their child’s diagnosis (Mackta and Weiss, 1994). In order to further describe the impact that ANE has on family’s lives, participants were asked to rank the changes made to their daily lives and plans for the future. When asked about the changes that participants have made to their daily lives after experiencing an ANE episode in their family the median response was 10 (8-10). Some of the reported changes included taking care of a child who has physical or intellectual disabilities as a result of an ANE episode, leaving their job to stay home and care for their child, financing increased costs of medical care, fear of infections, and the emotional toll of losing a child. When asked whether their plans for the future changed, the median response was 9.5 (5.5-10). Some of the changes reported include controlling children’s activities, choosing whether or not to have more children, and no longer travelling.

Changes in lifestyle and plans for the future did not seem to vary based on mutation status (p=0.56 and 0.97 respectively). Although not statistically significant, these changes did appear to vary based on the level of worry a participant had for their family members. The mean level of daily lifestyle
changes in participants who worry about their family members at least weekly was 9.10, for participants who worry less than weekly, the mean was 6.70 (p= 0.07). Daily lifestyle changes also seem to vary based on worry about children or future children. The median level of daily lifestyle changes in participants who worry about their children or future children at least weekly was 8.6 versus a mean of 5.5 in participants who worry about their children or future children less than weekly (p=0.02).

Parents often report concerns about the risks involved with vaccination and going to school during the flu season. In order to better determine the decisions that parents make regarding these issues, participants were asked about the vaccination and schooling choices they have made for their children. Most participants reported that their physician recommends their child receive an annual influenza vaccine (76.9%). One participant reported that their physician recommends an annual flu shot, but not flu mist. Of 14 responses, 71.4% reported that their child does receive an annual influenza vaccine and 64.2% reported that their child’s vaccinations are up to date. Although not statistically significant, these numbers did seem to vary slightly based on mutation status. Of 8 participants whose child has a known RANBP2 mutation, 100% reported that their child does receive an annual influenza vaccine and 50.0% reported that their child’s vaccinations were up to date. Only 33.3% of participants whose child does not have a known RANBP2 mutation reported that their child receives an annual influenza vaccine, and 16.7% reported that all of their child’s vaccinations are up to date.

Participants were asked what type of schooling they have chosen for their child who has ANE and also for their children who do not have ANE. Of 14 responses, most participants reported that they have chosen either private or public schooling for their child who has ANE (42.9%). Two participants (14.3%) reported that their children now attend specialized schools for children who have disabilities. The additional 42.9% of participants reported that their child is not of school age.

Regarding children who do not have ANE 35.7% (5/14) of participants reported that they do not have other children or that they are not of school age and 42.9% (6/14) have chosen to send their children to public or private school. No participants reported that they homeschool their children.
Discussion:

The main goal of this study was to document what families want and need out of a support network for ANE. Based on the results of this study, families are very interested in the development of an ANE support network, and would utilize the network often. Participants in this study reported the highest levels of interest in using the network to gain information about ANE and ANE research. Unexpectedly, the social aspects of a support network were considered less important to the respondents. Participants expressed their highest interest for communicating via an asynchronous online message board, as opposed to chat rooms or other online, synchronous forms of communication. This is consistent with two previous studies which found that participants in online support networks have a high level of interest in sharing information about their disease and posing and answering questions on an online message board (Coulson et al, 2007 and Cawdron and Issenman, 2002). Based on the survey results, the informational content of the support network should include ANE symptoms, prognosis, treatment and management, genetics and inheritance, and current ANE research.

Quantifying levels of worry and changes in lifestyle were helpful in determining other issues that should be addressed in an online support network. Based on the results of this study participants worry about their family’s health frequently, at least once a week. Their worry also increased in severity and frequency after a diagnosis of ANE in their family. Reye’s syndrome is similar to ANE in that it has a febrile trigger, is often unpredictable and can have debilitating long-term effects (Pauline et al, 1982). Consistent with the results of this study, mothers of children who developed Reye’s syndrome showed feelings of anxiety, depression and overprotective behavior for up to five years after the diagnosis (Pauline et al, 1982). Experiencing an acute and unexpected event, such as Reye’s syndrome or ANE, can cause families to lose their sense of security and feel the need to protect their children from having a recurrent episode. Although participants reported a higher level of interest in information about ANE,
communicating with other families and sharing their story were both ranked highly (8 out of 10). Information and an online message board may be adequate to address families’ worry about ANE and provide them with a way to communicate with each other. Further research will be necessary to determine effective forms of supportive communication between these families.

Because ANE requires an infectious trigger, it was expected that families would feel more worried when their children were put in situations that increase the chance of acquiring an infection. This was confirmed and further elaborated in this study. Participants seem to be the most worried about their family member who has ANE developing a cold or fever and during the winter/flu season. Their worries may seem irrational to persons unfamiliar with the disorder. A support network can help address these concerns by providing validation of their worries and could help inform the family and care providers about ways to protect their child during the flu season. A support network may provide families with the opportunity to discuss what they do when their child has a cold or fever. The opportunity to discuss these issues may help families feel more at ease with their decisions.

The results of this study show that families have made changes to their daily lives and future plans in response to an ANE experience. The results also show that participants who worry more frequently seem to report larger changes to their lives. Based on previous research, support network participants have reported that they gained feelings of enhanced social well-being and they felt better informed after using an online support group (Bartlett and Coulson, 2010). Family members of children with other genetic disorders report using support networks to share information on coping with their disorders and to regain a sense of personal control (Mackta and Weiss, 1994). Parents of children with ANE often make changes to their lives in order to protect their children from developing an infection or a fever. However, there are no guidelines for these situations and parents have expressed anxiety from not knowing whether they are doing the “right” thing (personal communication, Derek Neilson). Further research is necessary to determine if using a support network reduces families’ amount of worry, and possibly reduces the number of changes they make to their lives.
Based on the results of this study, families seem to be unsure about vaccinations. Influenza is the most common viral trigger for ANE episodes and school-age children have the highest incidence of influenza in most communities (Fiore et al, 2012). Currently, the World Health Organization (WHO) recommends that everyone over age the age of 6 months receive an annual influenza vaccine, with the exception of people who have had Guillain-Barre syndrome or are allergic to a vaccine component (WHO position statement on influenza vaccines(August 2005)). However, little research has been performed to determine the risk of influenza vaccines for children who are predisposed to influenza related encephalopathies. One study completed in Japan suggests that ending the mass immunization of school age children seemed to increase mortality from influenza related encephalopathies (Ono et al, 2003). These results may be reassuring, but families are still concerned about the risk involved with vaccinating children who are predisposed to ANE. This concern is not unreasonable. There has been one report of a 6 month old boy who demonstrated ANE symptoms after a DTP (cellular pertussis) vaccine. The AAP now recommends using the DTaP (acellular pertussis) vaccine because of a known risk of high fever and encephalopathy (Rorke-Adams et al, 2011).

Vaccinations were one of the highest sources of worry for families who have been affected by ANE. Results also showed that all participants who have a known mutation receive an annual influenza vaccination, but only one third of those who do not have a known mutation receive the vaccine. Interestingly, a larger percentage of participants reported that their child receives an annual influenza vaccine than those who reported that all of their child’s vaccinations were up to date. There are two possible explanations for these results. Some parents have chosen to spread the vaccine schedule over larger periods of time in order to prevent a vaccine related fever (personal communication, Derek Neilson). Also, the questionnaire did not specify whether this question included the influenza vaccine. Some participants may have reported that their child’s vaccinations were not up to date because their child had not yet received an influenza vaccine at the time that the questionnaire was sent (October, 2011). This result is difficult to explain because our questionnaire did not explore why parents may
choose to delay their child’s vaccinations. This study confirms that vaccinations are an area of concern for parents of children with ANE and further research is needed to fully delineate the concerns and the risks of vaccination in this population.

About 76% of participants reported that their physician recommended their child receives an annual flu shot. This shows that about one quarter of participants in this study either did not receive a recommendation about the influenza vaccine, or were told that their child should not receive the vaccine. Information about reactions to vaccinations should be included in a support network to provide consistent information for both families and physicians. More research in this area could help determine what physicians are recommending, what types of reactions children predisposed to ANE have had to vaccines, and what parents believe about the effects of vaccines.

The results of this study did not show large variation in responses between families who have a \textit{RANBP2} mutation, and those who do not have an identifiable mutation. These results show that a support network does not need to contain tailored information for both groups of families and that both would most likely benefit from the same support network information.

There were a few observations in this study that did not approach significance but, if they are replicated in further studies, may be very interesting. As expected, participants whose family member did not survive their ANE episode reported a higher frequency of worry about other family members than participants whose family member did survive. However, participants whose family member fully recovered from their ANE episode reported that they worry more frequently than those whose family member is living with long term effects. There are two possible explanations for this finding. It is possible that families are distracted by caring for their child who now has medical or developmental problems and are not worried about ANE. Also, this finding could be related to the age that the ANE episode occurred. The three participants whose family member fully recovered responded that their family member was between the ages of six months to two years. Further studies, with larger sample sizes
should be done to investigate the impact that ANE has on families related to the age that a child is
diagnosed with the condition.

Limitations

The results of this study are based on a small sample size, which is not uncommon when studying very rare disorders. Because this study was a voluntary, online questionnaire, the responses we received may be biased towards highly motivated families who support research and are information seekers. Multiple members from the same family were encouraged to respond to the questionnaire in order to increase the potential sample size. However, this also increases the likelihood that our results are representative of several family members from a small number of families. Finally, physicians were contacted first and asked to forward the study questionnaire to their patients. It would be difficult to determine the exact number of patients who actually received the questionnaire in order to calculate the response rate for this study.

Future Research

Future research should be done in order to help determine better management for children who are predisposed to ANE. A major concern for many families is whether or not to vaccinate their children. Research should also be done to determine the safety of vaccines, specifically to see if any children who are predisposed to ANE have had bad reactions to vaccines.

Conclusions:

The results of this study suggest that there is a high level of interest in using a support network to gather more information about ANE and current ANE research. Families expressed high levels of worry in response to an ANE experience, and have consequently made dramatic changes to their lives. Based on the impact that ANE has on the lives of families, this study suggests that an online informational and support network would be beneficial to families who are affected by ANE.
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### Table 1: Demographic Information

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<tr>
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<td>Yes</td>
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<td>8.00</td>
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<tr>
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<td>1</td>
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<td>35.00</td>
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Figure 1: Interest in 6 support network features (n=24)

- Emotional Support: Median Ranking 6.5
- Sharing your family's story: Median Ranking 8
- Communicating with other families: Median Ranking 8
- Fundraising for ANE research: Median Ranking 9.5
- Information about ANE research: Median Ranking 10
- Information about ANE: Median Ranking 10
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<th>Feature</th>
<th>Median (interquartile range)</th>
<th>Mutation vs no Mutation (P values)</th>
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<td>Information about ANE</td>
<td>10 (9-10)</td>
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<td>Information about ANE Research</td>
<td>10 (8.25-10)</td>
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<td>Fundraising for ANE Research</td>
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<tr>
<td>Sharing your family’s story</td>
<td>8 (6.25-9)</td>
<td>0.26</td>
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<tr>
<td>Communicating with other families</td>
<td>8 (4.5-10)</td>
<td>0.48</td>
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<td>Emotional Support</td>
<td>6.5 (3.5-9)</td>
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<td>Interest</td>
<td>Median Response (Interquartile Range)</td>
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<tr>
<td>-------------------------------------------------------------------------</td>
<td>---------------------------------------</td>
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<tr>
<td>Symptoms</td>
<td>10 (9-10)</td>
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<td>Prognosis</td>
<td>10 (9-10)</td>
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<td>Treatment and Management</td>
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<td>Genetic Testing and Inheritance</td>
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<td>Current ANE research</td>
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Figure 2: Sources of Worry Before and After ANE

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<tr>
<th>Source</th>
<th>Median Ranking Before ANE</th>
<th>Median Ranking After ANE</th>
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<td>Public Places</td>
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<td>5</td>
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<td>Public Transportation</td>
<td>1.5</td>
<td>6</td>
</tr>
<tr>
<td>School</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Vaccines</td>
<td>1.5</td>
<td>7</td>
</tr>
<tr>
<td>A Doctor's Office</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Winter/flu Season</td>
<td>2.5</td>
<td>9</td>
</tr>
<tr>
<td>Fever/Infection</td>
<td>4</td>
<td>10</td>
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</table>

Median Ranking (1-10)
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<tr>
<th></th>
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<th>After ANE</th>
<th>p values</th>
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<td>Median</td>
<td>Interquartile range</td>
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<td>1-2.75</td>
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<td>School</td>
<td>19</td>
<td>1</td>
<td>1-3</td>
</tr>
<tr>
<td>Going to the doctor's office</td>
<td>19</td>
<td>1</td>
<td>1-3</td>
</tr>
<tr>
<td>Winter/flu season</td>
<td>20</td>
<td>2.5</td>
<td>1-5.5</td>
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<tr>
<td>Vaccinations</td>
<td>20</td>
<td>1.5</td>
<td>1-4.5</td>
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<td>Having a cold or fever</td>
<td>20</td>
<td>4</td>
<td>1-6.75</td>
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Figure 3: Worry About Family Members Related to Survival

- Survived (n=15)
- Did not survive (n=4)

- Worry weekly
- Worry less than weekly

n
Figure 4: Worry About Children/ Future Children Related to Survival

Survived (n=12)

Did not survive (n=4)

- Worry weekly
- Worry less than weekly
Figure 5: Worry About a Recurrent ANE Episode Related to ANE Outcome

Long-term effects (n=12)

No long-term effects (n=3)

<table>
<thead>
<tr>
<th>n</th>
<th>Worry weekly</th>
<th>Worry less than weekly</th>
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</thead>
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</tbody>
</table>

27
Figure 6: Worry About Other Family Members Related to ANE Outcome

Long-term effects (n=12)

No long-term effects (n=3)

Worry weekly
Worry less than weekly

n
Figure 7: Worry About Children/ Future Children Related to ANE Outcome
Figure 8: Vaccination Decisions by Mutation Status

- No mutation (n=6)
  - All vaccines up to date
  - Influenza Vaccine

- Mutation (n=8)
  - All vaccines up to date
  - Influenza Vaccine

% Who receive vaccinations
Table 7: Frequency of worry based on mutation status

<table>
<thead>
<tr>
<th>How often do you worry that your family member will have another ANE episode?</th>
<th>Mutation n (%) (n=9)</th>
<th>No Identifiable Mutation n (%) (n=10)</th>
<th>p value</th>
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<td>At Least Weekly</td>
<td>6 (60.00)</td>
<td>6 (66.67)</td>
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<td>Less Than Weekly</td>
<td>4 (40.00)</td>
<td>3 (33.33)</td>
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<table>
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<th>How often do you worry that other members of your family might develop ANE?</th>
<th>n=9</th>
<th>n=11</th>
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<td>At Least Weekly</td>
<td>4 (44.44)</td>
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<td>Less Than Weekly</td>
<td>5 (55.56)</td>
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<table>
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<th>How often do you worry that your children (or future children) might develop ANE?</th>
<th>n=9</th>
<th>n=11</th>
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</thead>
<tbody>
<tr>
<td>At Least Weekly</td>
<td>5 (62.50)</td>
<td>6 (66.67)</td>
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<td>Less Than Weekly</td>
<td>3 (37.50)</td>
<td>3 (33.33)</td>
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Appendix B: Questionnaire:

1. What is your current age?
   - Under 18 ---> (End survey)
   - 18 – 27
   - 28 – 37
   - 38 – 47
   - 48 – 57
   - Over 57

2. What is your gender?
   - Male
   - Female

3. What country do you currently live in?
   - Drop down box with a list of countries

4. What is your highest level of education?
   - Grades 1-4
   - Grades 5-7
   - Grades 8-12
   - High school diploma/GED
   - Some college (no degree)
   - Associate’s degree
   - Bachelor’s degree
   - Master’s degree
   - Doctorate degree (MD, PhD, JD, DDS, DMD)
   - Other:_______________________

Acute Necrotizing Encephalopathy (ANE) is a rare disease that can occur after a fever related illness such as the flu. ANE can cause weakness, seizures, coma and brain changes. Young children are most frequently affected by ANE.

5. Have you or any of your family members had genetic testing for ANE? This test would be a blood test to see if an ANE event was caused by a change in one of your genes.
   - Yes
   - No
   - Do not know

6. Is there an ANE associated gene mutation that increases the risk of having ANE in your family?
   - Yes
   - No
   - Do not know

7. Have you or a family member had an ANE episode?
   - Yes
   - No ---> skip to #15
The following page will ask questions about your family member’s history of ANE.

8. The family member who has had an ANE episode is your______. Please choose only one answer.
   Self
   Spouse
   Brother/sister
   Grandchild
   Niece/nephew
   Cousin
   Other: __________

9. How old was your family member when he/she was first diagnosed with ANE?
   _____ years _____ months

10. How many ANE episodes has your family member had?
    1
    2
    3
    more than 3
    Do not know

11. Did your family member survive their ANE episode?
    Yes
    No-----> skip to #15
    Do not know----> skip to #15

12. What is your family member’s current age?
    _____ years

13. Does your family member have long-term effects from an ANE episode?
    Yes
    No
    Do not know

14. What effects does your family member have from ANE:

15. Would you be interested in a support network for families who are affected by ANE?
    Yes
    No ----> (end survey)
    Do not know
The following page asks questions about your interest in and preferences for an online ANE support network.

16. How often do you think you would access a support network for ANE?
   - Daily
   - Once or twice a week
   - Once or twice a month
   - Once or twice a year
   - Less than once a year
   - Never

17. How important would each of the following features of a support network be for you?
   (1= “not important” 10= “very important”)
   - Communicating with other ANE families
   - Emotional support
   - Sharing your family’s story with other families who are affected by ANE
   - Information about ANE
   - Information about current research for ANE
   - Fundraising for ANE research
   - Other: _____________

18. How important are each of the following forms of communication with other ANE families to you?
   (1= “not important” 10= “very important”)
   - Internet chatroom
   - Internet message board
   - Internet video discussion (such as Skype)
   - Telephone conversation
   - Other: _____________

19. How important is it to you that each of the following types of information about ANE be included in a support network?
   (1=“not important” 10=“very important”)
   - Symptoms
   - Prognosis
   - Treatment and management
   - Genetic testing and inheritance
   - Risk for future children
   - Current research
   - Other: _______________

20. In your opinion, who should have access to an ANE support network?
   - Only families who are affected by ANE
   - Families who are affected by ANE and health care professionals
   - Families who are affected by ANE, health care professionals and the general public
21. Would you like to be able to share pictures of yourself or your family member on an online ANE support network?
   Yes
   No
   Do not know

22. Would you like an online ANE support network to include links to networking websites (such as Facebook) for further communication with other ANE families?
   Yes
   No
   Do not know

23. What other features of an ANE support network would you like us to consider?

24. Some families have made changes to their lives because of ANE and some have not. The following asks about the impact ANE has had on you and your family. This information will be used to help tailor the support network to the needs of its members. Are you willing to answer these additional questions?
   a. Yes-----> continue
   b. No----- > end survey

   For the next 3 questions, “worry” will be defined as feelings of uneasiness or uncertainty related to ANE.

25. How often do you worry that you or your family member will have another ANE episode?
   More than once a day
   Once a day
   Once or twice a week
   Once or twice a month
   Once or twice a year
   Less than once a year
   Never

26. How often do you worry that additional members of your family might develop ANE?
   More than once a day
   Once a day
   Once or twice a week
   Once or twice a month
   Once or twice a year
   Less than once a year
   Never
27. How often do you worry that your children (or future children) might develop ANE?
   More than once a day
   Once a day
   Once or twice a week
   Once or twice a month
   Once or twice a year
   Less than once a year
   Never
   Not Applicable

28. What level of worry does ANE cause for you?
   (1= “no worry”  10= “very high worry”)

29. What level of worry does each of the following cause for you?
   (1= “no worry”  10= “very high worry”)
   Being in public places
   Using public transportation (planes, buses, trains etc.)
   Going to school
   Going to a doctor’s office
   Winter/flu season
   Getting vaccinations or flu shots
   Having a fever
   Not applicable

30. What level of worry did each of the following cause for you prior to a diagnosis of ANE in your family?
   (1= “no worry”  10= “very high worry”)
   Public places
   Public transportation (planes, buses, trains etc.)
   Going to school
   Going to a doctor’s office
   Winter/flu season
   Getting vaccinations or flu shots
   Having a fever
   Not applicable

31. How much has a ANE changed your daily life?
   (1= “no change”  10= “many changes”)
   Please explain:_________________________________________________

32. How much has ANE changed your plans for the future (education, career changes, recreation/travel, etc)?
   (1= “no change”  10= “many changes”)
   Please explain:_________________________________________________

33. Please describe any medical or lifestyle changes you have made due to ANE in your family:
34. Do you have a child/children?
   Yes-----> continue
   No-----> end survey

35. Are you the parent who is usually responsible for taking your child to doctor’s appointments and making most of the daily decisions about your child’s health and medical care?
   Yes-----> continue
   No -----> end survey

   The following page will ask questions about health behavior changes you have made in response to a diagnosis of ANE in your family.

36. Are vaccinations required in the country in which you live?
   Yes
   No
   Do not know

37. Is an annual influenza vaccine (flu shot or flu mist) required in the country in which you live?
   Yes
   No
   Do not know

38. What recommendations were made about the annual influenza vaccine (flu shot or flu mist) for your child who has ANE?
   It was recommended that my child receive an annual influenza vaccine of either type
   It was recommended that my child should NOT receive an annual influenza vaccine of either type
   It was recommended that my child should receive the flu shot but not the flu mist annually
   It was recommended that my child should receive the flu mist but not the flu shot annually
   No recommendations were made regarding the influenza vaccine
   Not Applicable

39. Does your child receive an influenza vaccine (flu shot or flu mist) each year?
   Yes
   No
   Do not know

40. Are your child’s vaccines (shots) up to date for a child of his/her age?
   Yes
   No
   Do not know
41. What type of schooling is available for children where you live? Check all that apply
   Public school
   Private school
   Boarding school
   Home schooling
   Other:__________________

42. What type of schooling have you chosen for your child who has ANE? Check all that apply
   Public school
   Private school
   Boarding school
   Home school
   My child is not old enough for school
   Other:_______
   Not Applicable

43. What type of schooling have you chosen for your children who have not had ANE? Check all that apply.
   Public school
   Private school
   Boarding school
   Home school
   My child is not old enough for school
   Other:_______
   Not Applicable