Hypokalemic Periodic Paralysis: A Model for a Clinical and Research Approach to a Rare Disorder

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Summary: Rare diseases have attracted little attention in the past from physicians and researchers. The situation has recently changed for several reasons. First, patient associations have successfully advocated their cause to institutions and governments. They were able to argue that, taken together, rare diseases affect approximately 10% of the population in developed countries. Second, almost 80% of rare diseases are of genetic origin. Advances in genetics have enabled the identification of the causative genes. Unprecedented financial support has been dedicated to research on rare diseases, as well as to the development of referral centers aimed at improving the quality of care. This expenditure of resources is justified by the experience in cystic fibrosis, which demonstrated that improved care delivered by specialized referral centers resulted in a dramatic increase of life expectancy. Moreover, clinical referral centers offer the unique possibility of developing high quality clinical research studies, not otherwise possible because of the geographic dispersion of patients. This is the case in France where national referral centers for rare diseases were created, including one for muscle channelopathies. The aim of this center is to develop appropriate care, clinical research, and teaching on periodic paralysis and myotonia. In this review, we plan to demonstrate how research has improved our knowledge of hypokalemic periodic paralysis and the way we evaluate, advise, and treat patients. We also advocate for the establishment of international collaborations, which are mandatory for the follow-up of cohorts and conduct of definitive therapeutic trials in rare diseases. **Key Words:** Ion channel, periodic paralysis, hypokalemia, rare disease, electromyography.

INTRODUCTION

We owe the recognition of periodic paralysis as a distinct entity and the understanding of its muscle origin to the early German school of the late 19th century. Early in the 20th century, physicians observed that decreased blood potassium levels occurred during attacks (historical review[1]) leading to a usable definition of the disease in clinical practice.

HYPOKALEMIC PERIODIC PARALYSIS: A MUSCLE DISORDER CAUSING EPISODIC MUSCLE WEAKNESS

Hypokalemic periodic paralysis (hypoPP) is characterized by reversible attacks of muscle weakness associated with decreased blood potassium levels.[2] There are several causes for this disorder; hypoPP can be secondary to renal or gastrointestinal potassium loss.[3] In this occurrence, abnormal blood potassium levels are also observed between attacks, and muscle weakness fluctuates in parallel with blood potassium levels. Muscle weakness is thought to be directly related to the degree of muscle depolarization induced by hypokalemia. In primary hypoPP, blood potassium levels are abnormal only during attacks. Two forms of primary hypoPP have been recognized: thyrotoxic hypoPP, which is associated with thyrotoxicosis, and familial hypoPP, which is a genetic disorder of autosomal dominant inheritance.

Thyrotoxic hypoPP is considered to be a complication of hyperthyroidism.[4] The frequency of thyrotoxic hypoPP is not known. It is present in all populations but occurs more frequently among Asians. Most cases are sporadic with a male predominance (9:1), but familial cases have also been anecdotally described. Patients usu-

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ally present with paralysis of the four limbs and a profound decrease in blood potassium levels (down to less that 1 mEq/L). Attacks may spontaneously recover and recur if thyrotoxocosis is not treated. In a number of cases, signs of hyperthyroidism are clinically obvious, although this is not always the case. In Caucasians, signs and symptoms of thyrotoxicosis are often absent. Attacks of hypoPP occur only during states of hyperthyroidism and never when thyroid function is back to normal. Therefore, treatment is based upon the restoration of a euthyroid state. In the meantime, potassium chloride may be administered to improve muscle force and prevent occurrence of new attacks. Some patients may also have some degree of glucose intolerance.

Thyrotoxic hypoPP is thought to be related to an increased activity of the sodium-potassium adenosinetriphosphatase (Na/K-ATPase) pump, which presumably causes an intracellular shift of potassium and hypokalemia.[4] A tentative hypothesis is that thyrotoxic hypoPP patients have a predisposition to the Na/K-ATPase pump activation by thyroid hormones or hyperinsulinism.

The alternate form of hypoPP is familial hypoPP, commonly referred to as hypoPP. The exact frequency of the disease is unknown: the prevalence has been estimated at 1:100,000 in Danish registries.[1]

Familial hypoPP is a monogenic disorder with an autosomal dominant mode of inheritance. Some cases may present as sporadic because of the incomplete penetrance of the disease, mostly in women.[5,6] The disease is potentially lethal. A mortality of 10% was common before the advent of intensive care units. Nevertheless, severe cases may still occur.[7]

Although the genetic defect is present throughout life, the age at onset is early in the second decade. The frequency of attacks is higher from the second to the fourth decades of life, and then tends to decrease. Attack frequency is very variable, ranging from once in a lifetime to several per week. Affected women tend to have fewer attacks than affected men, reflecting the decreased expressivity of the disease in women.

Attacks of muscle weakness usually affect the four limbs. When incomplete, they often predominate in the lower limbs. Respiration, deglutition, and ocular motility are usually spared but may be affected in the most severe attacks. Coughing is more difficult during attacks. Attacks usually occur several hours after strenuous exercise or a meal rich in carbohydrates. Typically, patients awaken in the night paralyzed. Attacks may also be milder, affecting one or more limbs. Attacks last several hours and resolve spontaneously. Recovery may be sped up by the ingestion of potassium chloride and may be aborted by pursuing exercise at a moderate level. If blood potassium levels are measured during an attack, they are found to be below the normal range. For diagnostic purposes, measurements of blood potassium levels are important. They can be performed in the emergency room or at home. Because serum potassium levels are normal between attacks, it is important for confirming the diagnosis to obtain measurements during an attack.

It is now well established that hypoPP does not affect the heart per se. Cardiac arrhythmias may be provoked by severe hypokalemia but the heart muscle as well as smooth muscles are not affected by the disease, as shown in two autopsied cases.[6] It can be hypothesized that reported cases of hypoPP with persistent electrocardiogram abnormalities between attacks were actually cases of Andersen-Tawil syndrome.[8]

PERMANENT MUSCLE WEAKNESS AND VACUOLAR MYOPATHY: OTHER FEATURES OF HYPOPP

A number of hypoPP patients develop permanent muscle weakness. The frequency of patients with permanent muscle weakness between attacks is not known. The presence of permanent weakness is well known to clinicians, as well as the variability of weakness from one examination to another. The significance of this permanent muscle weakness has been and is still debated, as discussed below.[9]

Permanent muscle weakness is rarely, but possibly, observed in young adults. It usually fluctuates. The patients are generally aware that they can partially control the intensity of the weakness by mild exercise, or by the ingestion of potassium chloride salts or acetazolamide tablets. In this circumstance, permanent weakness may indicate a state of persistent or continuously recurring mild attacks, and may be dramatically improved by long-term use of carbonic anhydrase inhibitors.[1,10-12]

In contrast, persistent muscle weakness is less fluctuating in older patients, and is less sensitive to medication. This lack of responsiveness to treatment is a sign of muscle degeneration, a fixed myopathy. The frequency of the myopathy is not well established. This is due to the fact that hypoPP patients rarely undergo a muscle biopsy and there is no reliable clinical imaging method to detect such a myopathy.[6] Some authors have proposed that it affects all patients over 50 years old to some degree.[9] Its severity is variable, ranging from weakness evidenced only at clinical examination but not interfering with a normal life in most patients, to wheel-chair bound patients. The myopathy arises independently of the frequency and the severity of the attacks. It can even occur in the absence of attacks.[6,13] The onset is usually in the fourth or fifth decade of life. The myopathy affects mostly the muscles of the pelvic girdle and the proximal muscles of upper and lower limbs.

Vacuoles are regularly seen on muscle biopsies and are considered the hallmark of the myopathy, which is termed a vacuolar myopathy. They are thought to be

markers of the myopathy, although vacuoles are seen in patients without a permanent muscle weakness. Vacuolar myopathy affects mostly muscles of the pelvic girdle and proximal muscles of upper and lower limbs. The origin of the vacuoles has been debated. Pathological studies suggest that the vacuoles arise from the sarcoplasmic reticulum and the tubular system as the result of proliferation and degeneration of these membranous organelles.[14,15] Several stages have been distinguished by pathological studies with different degrees of muscle fiber degeneration. Other morphologic changes are also observed in periodic paralysis. Tubular aggregates, which originate for the endoplasmic reticulum, are localized under the muscle fiber membrane. Other changes include an increase in central nuclei, abnormal variation in fiber size, fiber necrosis, and proliferation of connective tissue. There is no animal model of vacuolar myopathy. Therefore, the exact sequence of events and the pathophysiological link between the formation of vacuole and muscle degeneration are still not understood. HypoPP represents a good model to understand the relationship between an ion channel mutation, abnormal cellular excitability, and cell death.

Because there was no correlation in terms of severity between attacks and myopathy, it was proposed that attacks (periodic paralysis) and myopathy (evidenced by a fixed permanent weakness) may represent two independent phenotypes with different ages at onset, and varying penetrance and expressivity.[5,16] The factors, genetic or epigenetic, triggering and controlling the expression of these phenotypes are unknown.

MUTATIONS IN VOLTAGE-GATED CALCIUM AND SODIUM CHANNEL GENES CAUSE FAMILIAL HYPOPP

Several causes, such as a defect in potassium metabolism, have been advocated for hypoPP. In the late 1980s, the group of Rüdel and Lehmann-Horn in Germany developed a technique to record the electrophysiological activity from muscle biopsies of patients with neuromuscular diseases.[17] This technique enabled them to make the seminal observation that when decreasing the potassium concentration in the extracellular medium, they could depolarize the muscle cells, which correlated with paralysis.[17] In contrast, normal muscle cells became hyperpolarized when the extracellular potassium was lowered. This observation suggested that abnormal ion fluxes might be implicated, a hypothesis that was reinforced when the primary role of a sodium channel was demonstrated in the other form of periodic paralysis: hyperkalemic periodic paralysis by our group and others.[18-20] The same strategy used to identify the sodium channel in hyperkalemic periodic paralysis was applied to hypoPP. Large families were collected to enable linkage analysis. This approach is based on the fact that each gene is present in the genome at two copies with different forms (alleles). The segregation of the alleles of the gene can be traced through generations. The cosegregation of one allele of a specific gene with the disease indicates that the tested gene is causative (linkage). In the case of hypoPP, the most obvious candidates were potassium channels. It became quickly obvious that none of the alleles of potassium channels segregated with the disorder. The study was then enlarged with markers covering the whole genome. Surprisingly, the first genetic markers that cosegregated with the disease were in close vicinity with a voltage-gated calcium channel.[21] Soon after, mutations were found in the voltage-gated calcium channel *CACNA1S*, establishing it as the first hypoPP-causing gene.[22,23] The voltage-gated calcium channel is made of four homologous domains, each of them composed of six transmembrane segments. Remarkably, all mutations changed positively charged amino-acids arginines in the voltage sensor segment 4 (R528H or G in domain II, as well as R1239H of G in domain IV).[22-24] The phenotype associated with both mutations is grossly similar.[5,25] The penetrance is incomplete and tends to be lower in women and to depend on ethnicity, although this latter point needs confirmation.[5,25-29] These two mutation sites in the calcium channel which cause hypoPP have now been found in all studied populations.[5,25,26,28-32] Mutations have only been observed in familial hypoPP but not thyrotoxic hypoPP, although there are anecdotal reports of familial hypoPP revealed by thyrotoxicosis.[25,32,33]

The voltage-gated calcium channel lies within the T-tubules, which are intracellular invaginations of the muscle membrane. Their known role is to couple the action potential with the intracellular release of calcium from the sarcoplasmic reticulum through the activation of calcium channels termed ryanodine receptors. In hypoPP muscle fiber, the excitation-contraction appears to be normal.[34,35] Expression studies of mutated calcium channels have been technically difficult because of the poor expression of the muscle calcium channel in *in vitro* systems. They have shown minor abnormalities pointing to a loss-of-function effect (decreased current density and slowed activation).[36,37] Other studies on muscle fibers obtained from biopsies have pointed to a reduction of an inwardly rectifying or an ATP-sensitive potassium current.[38,39] Thus, although the mutations in the calcium channel have been known for more than 10 years, there is no clear understanding of how they could provoke muscle fiber paralysis induced by depolarization and hypokalemia.[40]

Genetic linkage studies rapidly established that hypoPP was genetically a heterogeneous disease. The study of large families, demonstrated by linkage analysis and mutation search, showed that mutations in the voltage-gated sodium channel also caused hypoPP.[41,42] This dis-

covery came as a surprise because it was already known that mutations in the voltage-gated sodium channel caused other forms of periodic paralysis. Since then, rare families with mixed phenotypes and voltage-gated muscle sodium channel mutations have been reported, showing that the border between hypoPP and other forms of periodic paralysis is not as tight as previously thought.[43,44]

The voltage-gated sodium channel belongs to the same channel family as the calcium channel and shares a similar organization. It is made of four homologous domains, each of them composed of six transmembrane segments. Mutations causing hypoPP notably lie in different regions of the sodium channel than those causing other forms of periodic paralysis. Interestingly, they affect similar amino acids to those mutated in the calcium channel. They indeed change arginines in position 669 and 672 in the voltage-sensor S4 of domain II,[41,42,45] as well as in position 1132 in the voltage-sensor S4 of domain III.[46] These mutations have been found in all populations studied so far, but at a lower frequency than the one observed for calcium channel mutations (10 vs 60%).[45,47,48] The penetrance of sodium channel mutations is probably higher than the one observed for calcium channel mutations, at least in the only large family studied so far.[45] Differences have been noted in the phenotype displayed by patients bearing calcium or sodium channel mutations. In patients with sodium channel mutations, hypoPP tends to begin later, is accompanied by muscle aches, shows a predominance of tubular aggregates compared with vacuoles in the muscle biopsy, and is aggravated by acetazolamide.[45,49]

The mutations in the sodium channel causing hypoPP have been introduced by *in vitro* mutagenesis in the channel and both mutant and control channel have been expressed in *in vitro* systems. Biophysical parameters suggest a loss of function effect, an enhanced slow inactivation being most frequently observed, in contrast with sodium channel mutations causing other types of periodic paralysis where a gain-of-function was demonstrated.[42,46,49-51] Accordingly, recording of muscle fibers obtained from muscle biopsies showed a reduced current density and a slower upstroke and decreased action potentials when compared with controls.[42] As for the calcium channel, these observations are insufficient to understand how sodium channel mutations could provoke muscle fiber paralysis induced by depolarization and hypokalemia.

ARE MUTATIONS OF THE GENE ENCODING POTASSIUM CHANNELS ASSOCIATED WITH PERIODIC PARALYSIS?

It is now well established that mutations of potassium channel genes are responsible for some forms of periodic paralysis. Mutations in the potassium channel gene *KCNJ2* have indeed been established as one of the causes of Andersen-Tawil syndrome, which is associated with distinctive facial features, and electrocardiographic abnormalities.[52]

The implication of potassium channels causing other forms of periodic paralysis has been debated. The *KCNE* genes represent a family of genes encoding for Mink-related peptides that are single transmembrane proteins, inactive on their own but which bind and modulate biophysical properties of potassium channel pore-forming units. Based on a preferential expression in skeletal muscle, Abbott and colleagues[53] proposed that Mink-related peptide 2 (from *KCNE3*) forms a complex with Kn3.4, a Shaw-type potassium channel, which results in a complex that recapitulates biophysical and pharmacologic properties of potassium currents implicated in the resting potential in skeletal muscle. Abbott and colleagues also considered *KCNE3* as a candidate for hypoPP.[53] The authors looked for DNA variants in the *KCNE3* gene and found a missense mutation that changed an arginine into a histidine at amino acid 83. This missense mutation was absent from 120 control individuals. It was present in three members of a family with hypokalemic periodic paralysis and segregated with the disease within the family. The same mutation was also present in two members of another family with an unspecified type of periodic paralysis. Moreover, when expressed in rodent skeletal muscle cell, the mutant changed the excitability of muscle cells by producing depolarization.[53] In support of this first observation, the mutation was also found in 1 of 15 patients with the thyrotoxic form of hypoPP.[54] However, the latter observation was not reproduced in the Chinese population.[55]

At first glance, these observations seem to be solid enough to establish *KCNE3* as a causative gene for hypoPP. However, it must be noted that they were established in too small a number of patients to enable statistical analysis and that the number of controls was low, even if considered as adequate under current standards. The study of large collections of controls and patients changed the view on the role of *KCNE3* in hypoPP. Indeed, no other variant of the *KCNE3* gene was ever associated with periodic paralysis in contrast to other ion channel genes. In addition, the mutation was found to be associated in the same patient with a sodium channel mutation well known to cause hypoPP.[56] The phenotype of the patient who had both a potassium channel and a sodium channel mutation was similar to that of his father who carried only the sodium channel mutation, demonstrating that the potassium channel mutation did not breed true in contrast to the sodium channel mutation. The R83H mutation was also found at the same frequency in large groups of controls or periodic paralysis patients (approximately 1%).[56,57] Altogether, these ob-

servations argue against a causative role of the R83H mutation of the *KCNE3* gene in periodic paralysis. The R83H mutation should therefore be considered as a variant of unknown role. It is possible that this variant may play a role in skeletal muscle physiology.[58] Genetic analysis in patients with periodic paralysis, however, clearly shows that its putative role is not causal.

The *KCNE3* story is of general interest to those involved in ion channel disorder studies. The major genes have been identified by linkage analysis, and mutation screening in genes identified by linkage analysis. This requires large families. Cases of periodic paralysis, in which no mutation is found in one of the known genes, frequently occur as sporadic cases or in families too small to perform linkage analysis. The *KCNE3* story has shown that, in this particular situation, the demonstration of the absence of mutation in a group of controls as well as functional expression of the mutated channel are not sufficient to demonstrate the causative role of the suspected gene in the absence of other mutations.

The *KCNE3* story also points to a paradox in muscle ion channel disorders. For the researcher, the advantage of working on ion channels comes from the extensive knowledge of their mechanism of action. It was inferred that one could rapidly go from the identification of the gene defect to the understanding of pathophysiology. It was hypothesized that ion channel mutations would lead to biophysical defects detectable by the expression of mutants in *in vitro* systems, and conversely that biophysical defects would be predictive of the role of ion channels in diseases. This turned out to be true for hyperkalemic periodic paralysis but not for hypoPP. It is now well established that mutations in the voltage-gated calcium channel cause the most frequent form of hypoPP. The biophysical consequences of the mutations are modest if any. For *KCNE3*, the R83H variant causes drastic changes in membrane excitability but is not a causative factor for hypoPP.

This observation points to the fact that even if we are able to reconstruct current by expressing channel subunits, this is far from being sufficient to link a mutation to a phenotype. Membrane excitability is a subtle function with multiple players. How the latter interact in the presence of the mutation and how this interaction leads to the phenotype remains to be elucidated. The identification of the causative genes has been a major leap for the understanding of this disease. There is, however, no direct link between the gene defect and the complexity of the pathophysiology, which still needs to be deciphered.

IN VIVO FUNCTIONAL STUDIES OF MUSCLE ION CHANNEL MUTATIONS IN PATIENTS

The functional consequences of ion channel mutations on muscle membrane excitability in patients can be studied by the noninvasive technique of electromyography (EMG). During attacks of paralysis in hypoPP, the muscle membrane has been shown to be depolarized and unable to respond to electrical stimulation.[1] Between attacks, the muscle membrane activity recorded by EMG is normal, although muscle conduction velocities are decreased. Muscle conduction velocities have been recorded by invasive and noninvasive techniques. Invasive techniques have been shown to be more sensitive but less feasible in a daily practice. Interestingly, muscle conduction velocities were shown to be decreased in patients with different types of calcium mutations and proposed to be a marker for carrier status.[16,59-61]

Because muscle weakness may be triggered by exercise, it has been proposed to use strong and sustained voluntary contraction as a provocative test for diagnosis.[62] Surface-recorded muscle responses to supramaximal nerve stimulation are used to monitor muscle membrane activity and are considered to reflect muscle membrane activity. Analysis of the compound motor action potential (CMAP) amplitude before and at various times after long (5 min) exercise provides information on changes in the number of active fibers, and on their ability to depolarize and repolarize. A significant decrease in the CMAP amplitude after a long exercise test has been reported in $\sim$ 70–80% of the patients with periodic paralyses.[62,63]

We recently investigated patients with known ion channel mutations associated with different forms of periodic paralysis. Inclusive EMG allowed us to establish consistent links between the clinical syndromes and the muscle electrical response to different provocative tests (repeated short exercise, long exercise). In addition, statistical analysis of the results obtained from several patients carrying the same mutation provided evidence for the EMG changes caused by specific ion channel mutations. Overall, our results suggest that extensive EMG may help guide clinicians toward a specific ion channel gene defect, especially if access to genetic screening is limited.[64]

Fournier and colleagues[64] proposed a new classification for EMG patterns in patients with muscle channelopathies. Periodic paralysis patients could be divided into two groups defined as patterns IV and V. The decline in CMAP response, which occurs 15 to 20 minutes after completion of a long exercise, is a common feature to both patterns. This loss of muscle excitability correlates well with muscle weakness experienced by patients after strenuous exercise. An early incremental effect of repeated short exercise or long exercise on CMAPs was specific to patients with hyperkalemic periodic paralysis (pattern IV). Recording of a late CMAP decline after long exercise without preliminary increment (pattern V) is most consistent with mutations in *CACNA1S* or in *SCN4A*.[64] A similar pattern has been observed in patients

with mutations in *KCNJ2*.[65] This suggests that hypokalemic periodic paralysis-associated calcium channel mutations and Andersen-Tawil syndrome-associated *KCNJ2* mutations may lead to muscle membrane hypo-excitability through a common mechanism.[65]

TREATMENT AND CARE OF HYPOPP PATIENTS

Patients learn to decrease the number of attacks by having a balanced diet and avoiding meals rich in carbohydrates. Mild and regular exercise is also beneficial, and continuing to exercise mildly may help abort impending attacks. The use of potassium chloride salts may also be helpful to prevent or abort attacks. Based on the simple reasoning that diuretics inducing hypokalemia may be useful in hyperkalemic periodic paralysis, acetazolamide, an inhibitor of carbonic anhydrase, was tested with success by McArdle.[1] A patient suspected of having the hyperkalemic form of periodic paralysis but eventually diagnosed as having hypoPP unexpectedly reported a remarkable beneficial effect of acetazolamide on attack frequency.[66] The mechanism of action of acetazolamide is unknown; it may act on potassium channels implicated in regulating muscle excitability.[67] In addition, acetazolamide also improves muscle force when permanent weakness is present.[10-12] The efficacy of carbonic anhydrase inhibitors, such as acetazolamide or dichlorphenamide, on the frequency of attacks has not only been demonstrated in small series of patients but also in a multicenter, double-blind, randomized, placebo-controlled crossover trial.[68] An international multicenter trial coordinated by R.C. Griggs (University of Rochester, Rochester, NY) is under preparation to test the efficacy of carbonic anhydrase inhibitors, not only on the frequency of attacks but also on permanent muscle weakness. It may help to assess whether carbonic anhydrase inhibitors are effective in preventing the occurrence of a vacuolar myopathy. This international collaboration should stand as an example for rare diseases. The rarity of the disorders makes large international collaborations mandatory for therapeutic progress.

Some patients worsen with the use of acetazolamide.[69] It is now known that most of these patients display a sodium channel mutation.[45] However, on an individual basis, it is impossible to predict the response of a patient to acetazolamide, even when knowing the causative mutation.[70] Although a majority of patients with sodium channel mutations do not respond or are aggravated by acetazolamide, some patients still respond positively. The drug therefore merits a trial under strict medical supervision.[70] Mechanisms that could explain such a differential therapeutic response in patients bearing the same mutations are not known.

There are some anecdotal reports of the association of hypoPP and malignant hyperthermia. The question of the association of hypoPP and malignant hyperthermia arose from the difficulty of interpreting unambiguously *in vitro* contracture tests in muscle disorders caused by ion channel mutations.[71] We now know that malignant hyperthermia and hypoPP are different diseases caused by distinct mutations in the same gene; the voltage-gated calcium channel *CACNA1S*.[72,73] Some precautions should be taken during anesthetic procedures in hypoPP patients: intravenous glucose should be avoided and the temperature of fluids and their ionic composition should be carefully monitored.[74,75] Spinal anesthesia in hypoPP is safe, although a known cause of hypokalemia.[76]

CONCLUSION

In the past 15 years, the combination of advances in genetics, molecular, and clinical physiology has greatly improved our understanding of hypoPP. The complex links between an ion channel mutation and a phenotype remain to be unraveled. Ion channel mutations are not only responsible for a functional defect of the muscle membrane, but also cause muscle degeneration. HypoPP may therefore be a good model to decipher the pathway connecting an ion channel mutation to cell toxicity. The collaboration of referral centers on an international basis will allow the gathering of data from large numbers of patients that are necessary to accurately describe the natural history of these disorders, which is essential for the conduct of therapeutic trials.

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