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COMMENTARY

Brain Abnormalities in *PIK3CA*-Related Overgrowth Spectrum: Physician, Patient, and Caregiver Experiences

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ABSTRACT

PIK3CA-related overgrowth spectrum (PROS) disorders are caused by somatic, gain-of-function mutations in *PIK3CA* (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha) that result in hyperactivation of the phosphatidylinositol-3-kinase (PI3K) signaling pathway. PROS encompasses a broad spectrum of overlapping phenotypes that vary considerably in their severity and tissue distribution, leading to different and complex experiences for affected children and their families. The parent of a child with the PROS disorder megalencephaly-capillary malformation (MCAP) coauthored this article. MCAP is characterized by significant neurological involvement, and she describes personal experiences with this condition, including delays associated with obtaining a correct diagnosis, finding an experienced care team, challenges with schooling, medical complications, and the ongoing emotional and financial impacts on their lives. A physician perspective, which reinforces the challenges faced by the young child and his family, is provided by a clinician and researcher specializing in PROS disorders with central nervous system involvement. The physician reviews the mechanism of disease, some of the challenges in accurately diagnosing PROS conditions, disease-related complications, current treatment options and their limitations, and emerging therapeutic options including ongoing clinical trials. Our objective is to share these experiences and insights to benefit patients with PROS disorders, their families, and health care professionals involved with caring for patients with PROS.

Keywords: Megalencephaly-capillary malformation; Mosaicism; *PIK3CA*; PI3K; PROS

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Key Summary Points

As a result of the rareness of *PIK3CA*-related overgrowth spectrum (PROS) disorders, the experience and challenges of caring for patients with these disorders (especially those affecting the brain) are not well described in the literature.

This article is coauthored by the parent of a child with megalencephaly-capillary malformation (MCAP, which is a PROS disorder characterized by significant neurological involvement) who describes the challenges associated with this condition, including delay in diagnosis, finding a care team, and the ongoing impacts on her family.

The perspective of a physician with experience treating PROS disorders affecting the brain offers insights into the mechanism of disease, challenges in diagnosis, and disease-related complications.

Effective treatment options for PROS conditions are limited, and further research is needed to define optimal treatment plans and identify effective therapies to treat the disease and improve patients' quality of life in this chronic and multisystem disorder.

PATIENT AND CAREGIVER PERSPECTIVE

Diagnosis and Impact of Initial Interventions

My pregnancy was largely uneventful. My alpha-fetoprotein levels were elevated, and I suffered from polyhydramnios, but my doctor was not concerned. My pregnancy was the result of in vitro fertilization, and I was being closely monitored throughout the entire time. The embryos had been frozen for 3 years prior. At 35 weeks, my water broke and our son was delivered via C-section shortly thereafter. My doctor commented on his webbed toes and large size (3.6 kg), but nothing seemed worrisome at that time. He was transferred immediately to the neonatal intensive care unit out of an abundance of caution, but he appeared to be doing well. His clinical picture changed the following day when I was informed by the neonatologist that he likely had an unknown syndrome, and it was possible we would never know his exact condition. Our pediatrician examined him and printed a few articles on possible syndromes, one of which was megalencephaly-capillary malformation (MCAP). My husband and I met with the geneticist the next day and answered questions to try to determine what condition we were dealing with. An ultrasound examination was performed, and the results determined that all of his major organs were functioning properly. He had an atrial septal defect, ventricular septal defect, and jaundice, but overall he was a healthy baby. We were sent home a week later with many questions, but few answers, and numerous visits were planned with specialists.

My husband and I underwent genetic testing, as did our son, but no abnormalities were discovered at that time. Our son was tested for Beckwith-Wiedemann syndrome, but the results were negative for that disorder. Nine months after his birth, we were frustrated and still searching for a diagnosis. We began seeing another geneticist, who was also a neurologist, who diagnosed our son with MCAP on the basis of clinical features. At that time there were no commercial genetic tests available to confirm MCAP, so we sent blood and saliva samples to Dr. Mirzaa in Seattle for testing owing to her expertise in researching this disorder. A year and a half later we received confirmation from Dr. Mirzaa that our son did indeed have MCAP, but because there were no known therapies, we would have to closely monitor him. Learning that we would need to follow a "watch and wait" approach was anticlimactic. I somehow thought that if we had a confirmed genetic diagnosis, then we would have more answers, but we were told that MCAP is a highly variable

spectrum, and no two children were affected the same way.

We met several specialists and began the recommended screening and surveillance protocol for MCAP. That guidance meant ultrasounds were performed every 3 months to check for Wilms' tumors, and magnetic resonance imaging (MRI) of the brain and spine was performed annually. At that point we discovered that he had a large Chiari malformation, but because the decompression surgery was so dangerous, we would need to continue to closely monitor for symptoms. Our watchful waiting continued. We utilized a state program, the Tennessee Early Intervention System (TEIS), that provides services at no cost to families for eligible children with disabilities or developmental delays. That program allowed us to begin seeing occupational, speech, and physical therapists every day. He was hitting milestones and making progress, but it always felt like we were waiting for new issues to arise. He was the happiest baby, which made it easier for us to cope with the unknown. During this time I found a Facebook group for MCAP and was finally able to relate to other parents trying to navigate this syndrome. It was a light in a very dark time for us.

Managing Symptoms and Complications

The next few years were encouraging. Our son began to walk, started going to preschool, and continued to be the happiest kid around. We were still doing annual MRIs and ultrasounds, still receiving therapies in a school setting, and had undergone seven rounds of Candela laser surgeries to address a port-wine stain on his face. He had delays but was mostly able to communicate his needs and wants. He went to kindergarten and was in a mainstream class. While his delays were apparent, he was surpassing my expectations for him. For a time, I believed that he may be actually able to live independently at some point in his life.

The day after his seventh birthday, we went to the doctor for a wellness visit and left with a diagnosis of type 1 diabetes. This new development turned our world upside down. We were referred directly to an endocrinologist and our son began receiving insulin injections that day. Other children with MCAP struggle with hypoglycemia, but this was unexpected for us. After more endocrine tests were performed, our son was also diagnosed with secondary adrenal insufficiency, which is also common in MCAP. He now depends on two different drugs that he must take daily to stay alive. Every day it is a challenge to keep his blood sugar consistent and in range, and no 2 days are ever the same. My hopes of him living independently were shattered. I now am concerned that his health will continue to decline as he gets older, and more issues arise. As he matures, he understands that he is different, and we are starting to have conversations about his future. We are uncertain of his capabilities, which makes us question ultimately what our goals are for him. With an unknown life expectancy, we do not know how to manage our expectations. This makes things stressful for us as parents, and to his siblings as well, who are very observant.

I am frequently asked by clinical staff if I am in the medical profession. Not by choice! I have been forced to educate myself about MCAP, and I oftentimes educate our son's doctors as well. I am his advocate above all else, and I have to be aggressive sometimes to ensure he gets what he needs. When I discussed our son's diagnosis with Dr. Mirzaa, it was incredibly educational for me to learn about his specific *PIK3CA* (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha) mutation and how that correlated to his health. It was also refreshing to speak to a physician who was familiar with the syndrome and who had done such extensive research. Once again, I was encouraged. We began seeing a vascular team at Vanderbilt University that also had seen other children with PROS disorders, and now, finally, we feel like we are on the right track. It certainly has been a learning experience, and we have had good experiences and bad. Now that the medical community is becoming more aware of PROS and developing therapies to address these disorders, I no longer feel such despair and isolation with this syndrome.

Future Challenges

The COVID-19 pandemic has placed additional stress on our family. Before restrictions were in place as a result of the pandemic, we were making good progress with his schooling and educational needs. He has an individualized education plan (IEP) that ensures he receives necessary therapies and special education services, but because he has not been in school for a year and a half, we are facing unique circumstances. He has a compromised immune system, so he will not be able to go back to school until he is fully vaccinated. He has an educator that comes to the house twice a week for 3 h. Any strides that we had made prior to the pandemic were lost because of his inability to keep up during online classes. As he gets older and schoolwork becomes more difficult, the gap widens, and his delays become more pronounced. When he returns to school in person, it will require a lot of work for him to catch up to the other students. Right now, it is most important that he is healthy and that we keep him isolated until we can have him vaccinated.

In the past, my husband and I typically spent over US $10,000 per year on our son's medical costs alone. Our state of Tennessee is now offering Katie Beckett grants to those who qualify, so we were able to receive financial assistance this past year. We have managed to stay out of the emergency room because our son has been staying at home, but we are still faced with increasing medical costs. Our vascular team referred us to several specialists because our son had not been seen in some time, and new issues continued to arise. The cardiologist found a leaky valve; the ear, nose, and throat specialist discovered obstructive and central apnea; and our latest MRI showed a syrinx had developed on his spine. We are still watching and waiting.

Anticipation of Potential New Treatment Options

When I heard about alpelisib through our MCAP Facebook group, I was elated. Alpelisib, in combination with fulvestrant, is a drug approved for a specific form of breast cancer [15]. Because of its mechanism of action, it was being investigated for the treatment of PROS disorders but was not yet approved for use in patients with PROS. I immediately contacted our geneticist/neurologist and set up an appointment. When we asked him about alpelisib, he was a bit skeptical that it could help our son, and he did not follow up with our requests to learn more. I continued to follow the stories of others in our group and the progress being made by those receiving the drug through compassionate use. It is so encouraging to see that others are seeing positive results with this drug and that pharmaceutical companies are paying attention to our rare disease. When we met with the vascular team, they said that they were investigating the use of alpelisib in their patients with PROS and that it may be an option for us. I was finally getting the answers I so desperately wanted. As we continue to learn more about PROS, I am cautiously optimistic about the future and what that means for our son. I feel like a weight has been lifted and that I can be hopeful again. Although I do not know what the future holds for us, I am grateful that the medical community has taken an interest in PROS and that others will have the benefit of emerging drug therapies.

CLINICIAN PERSPECTIVE

Disease Background

PROS is a broad term that describes a heterogeneous group of disorders characterized by overgrowth and other malformations arising as a result of somatic gain-of-function variants in the *PIK3CA* gene, which encodes the α isoform of the catalytic subunit of phosphatidylinositol-3-kinase (PI3Kα) [7, 14, 17]. These mutations lead to hyperactivation of the PI3K (phosphatidylinositol-3-kinase) signaling pathway [7, 17] which in turn influences the activity of downstream effectors such as protein kinase B (AKT) and mammalian target of rapamycin (mTOR), leading to abnormalities in cell proliferation and growth of a wide range of cells and tissues [5, 7, 14, 17] (Fig. 1).

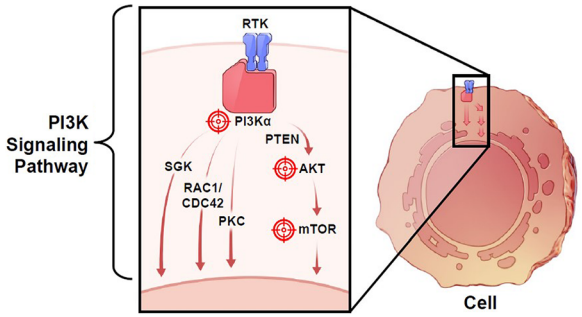

Fig. 1 PI3K signaling pathway. Gain of function mutations in *PIK3CA* result in increased PI3Kα activity, leading to abnormal cell function. Several drugs that target proteins in this pathway are being investigated for use in treating PROS disorders, including sirolimus (mTOR), miransertib (AKT), and alpelisib (PI3Kα). *AKT* protein kinase B, *CDC42* cell division control protein 42 homolog, *mTOR* mammalian target of rapamycin, *PI3K* phosphatidylinositol-3-kinase, *PI3Kα* phosphatidylinositol-3-kinase catalytic subunit alpha, *PIK3CA* phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha, *PKC* protein kinase C, *PROS* *PIK3CA*-related overgrowth spectrum, *PTEN* phosphatase and tensin homolog, *RAC1* Ras-related C3 botulinum toxin substrate 1, *SGK* serum- and glucocorticoid-inducible kinase. Reprinted from Canaud et al. [1]. Licensed under a Creative Commons Attribution 4.0 International License, https://creativecommons.org/licenses/by/4.0/

PROS disorders are highly variable from one another and between affected individuals; some disorders result in isolated or focal abnormalities, and others involve multiple organ systems including the central nervous system (CNS; [5, 7, 8, 14]). PROS disorders with brain involvement specifically include MCAP (or M-CM), hemimegalencephaly (HMEG), dysplastic megalencephaly (DMEG), and focal cortical dysplasia (FCD) [10, 11]. MCAP is characterized by several brain abnormalities, including diffuse or focal overgrowth of the brain and cortical malformations including polymicrogyria and focal cortical dysplasia [11]. Other clinical findings associated with MCAP include cutaneous capillary malformations with focal or generalized overgrowth, digital anomalies such as syndactyly and polydactyly, connective tissue laxity, and tone abnormalities [11].

If PROS is suspected clinically, the initial steps to diagnosis are a comprehensive physical examination and evaluation of the child's clinical features. Brain involvement manifesting with early onset megalencephaly may be detected by prenatal ultrasound or on examination at birth. Somatic overgrowth may be observed either at birth or early during the neonatal period. Because of the potential for multiple tissues and organ systems to be involved, it is prudent to perform thorough neurologic, skin, cardiac, abdominal, and musculoskeletal evaluations. To determine the extent of brain involvement, detailed neurological and neuropsychological assessments are almost always required. In the case of suspected MCAP, baseline brain and spinal cord imaging by MRI should be performed to detect cortical malformations (including cortical dysplasia), ventriculomegaly, and cerebellar abnormalities (including cerebellar tonsillar ectopia), if present. Because PROS shares clinical characteristics with other overgrowth syndromes, differential diagnoses that may be considered include the megalencephaly-polymicrogyria-polydactyly-hydrocephalus (MPPH) syndrome, Beckwith-Wiedemann syndrome, *PTEN*-related overgrowth disorders, Sotos syndrome, and others [11].

Tentative diagnosis of a PROS condition such as MCAP should be confirmed by genetic testing for pathogenic variants of *PIK3CA* [11]. The ability to detect a *PIK3CA* mutation is dependent on the ability to obtain a sample of affected or lesional tissue; biopsy may be scheduled to coincide with a required surgical procedure. Because of the mosaic nature of PROS disorders, high-depth, next-generation sequencing is the preferred sequencing method [13]. If a biopsy is not feasible, buccal swab testing or blood-based testing may be used, although the yield is expected to be lower in these peripheral tissues, especially blood, and a low-level mosaic mutation may not be detected [9]. However, failure to detect a *PIK3CA* variant does not exclude the diagnosis based on clinical characteristics [11]. My coauthor's son was clinically diagnosed with MCAP prior to confirmation of a *PIK3CA* mutation.

Disease-Related Complications

Neurosurgical complications associated with MCAP syndrome include ventriculomegaly, hydrocephalus, and cerebellar tonsillar ectopia or Chiari malformations [11]. Anatomical anomalies may include asymmetry due to somatic overgrowth, connective tissue dysplasia, distinct, dysmorphic facial features, and orthopedic complications. Hypotonia is present in a fraction of affected individuals. Cortical malformations, including specifically polymicrogyria and focal cortical dysplasia, are associated with increased risk of epilepsy, which is observed in approximately 30% of patients with MCAP and can vary widely in severity, onset, types of seizures, and response to treatment [11, 13]. Some children may experience a limited number of mild seizures and do not require long-term antiepileptic therapy. Others may be more severely affected and may require long-term antiepileptic therapy [6]. Other systemic complications are common and may include cardiovascular anomalies, endocrine issues, and gastrointestinal problems. Most patients with MCAP have capillary vascular malformations, often in the mid-facial area, and generalized capillary malformations are also common [12, 13]. Glucose dysregulation including hypoglycemia may arise as direct consequences of PI3K pathway hyperactivation. Developmental delay and intellectual disability are common in children with MCAP. These complications may range from mild to severe. Additionally, behavioral problems including autism and attention deficit hyperactivity disorder and others occur in a fraction of affected individuals. These behavioral and developmental problems add to the burden experienced by families seeking care for their children.

Treatment Approaches

At present, alpelisib is the only approved systemic therapy for PROS disorders [16]. Current treatment options are focused on individual manifestations and symptoms. Because of the urgent need for treatment options for PROS, an international expert consensus statement on

Table 1 Multidisciplinary care team needed for children with neurological involvement in PROS

Specialty	Role in diagnosis and/or management
Geneticist	Comprehensive diagnostic assessment, confirm *PIK3CA* mutation, genetic counseling
Pediatrician	General care, referral to specialists
Neurologist or epileptologist	Neurologic evaluation, management of neurologic complications including epilepsy
Neurosurgeon	Consideration of ventriculoperitoneal shunt or endoscopic third ventriculostomy to correct hydrocephalus; posterior fossa decompression may be considered for Chiari malformations; epilepsy surgery may be considered to treat epilepsy caused by focal or epileptogenic brain malformation
Orthopedic or vascular surgeon	Treatment of overgrowth (depending on nature, location, and severity)
Endocrinologist	Assessment and treatment of hormonal complications such as growth hormone disorders, hypoglycemia, and thyroid problems
Vascular anomalies specialist	Assessment and treatment of vascular and/or lymphatic malformations
Cardiologist	Evaluation and treatment of cardiovascular disease and arrythmias
Orthopedic specialist	Evaluation and management of focal somatic overgrowth, leg length discrepancy

Table 1 continued

Specialty	Role in diagnosis and/or management
Neurodevelopmental pediatrician	Assessment of neurodevelopmental and neurobehavioral issues
Developmental therapists	Offering developmental therapies (physical therapy, occupational therapy, speech therapy, and others)

PIK3CA phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha, *PROS PIK3CA*-related overgrowth spectrum

the standard of care for patients with PROS was recently published and covers somatic overgrowth, CNS abnormalities, seizures, endocrinopathies, neurodevelopmental issues, and vascular anomalies [3]. Because of the broad range of affected tissues and complications, coordinated care from a multidisciplinary team is required to tailor treatment to each patient's needs (Table 1). Patients with significant somatic and vascular/lymphatic abnormalities often require treatment at a vascular anomaly center or other major academic site but may not have access to this level of specialized care. Further, children with significant neurological involvement require treatment at a center that combines expertise in neurology (epilepsy), genetics, neurosurgery, neurodevelopment, and neuropsychology. Such multidisciplinary expertise may be challenging to find for affected families.

Routine monitoring for patients with PROS varies according to PROS severity and involvement and should include a comprehensive medical history, neurologic evaluation, and assessment of breathing or sleep problems. As patients with HMEG and MCAP with polymicrogyria are at risk of epilepsy, neurologic evaluation in these patients should include seizure assessment and need for antiepileptic medication and/or epilepsy surgery. Recommended imaging in children includes brain MRI every 6 to 12 months for 2 years, then yearly until age 6 to 8 years to screen for neurosurgical complications such as ventriculomegaly, hydrocephalus, cerebellar tonsillar ectopia, and Chiari malformation [11].

Emerging Treatment Options and Ongoing Clinical Trials

Systemic therapies are being explored in PROS conditions using agents targeting the PI3K pathway (e.g., mTOR, AKT, and PI3Kα inhibitors) [1]. Sirolimus, a targeted inhibitor of mTOR, has been investigated as a treatment option for patients with a variety of vascular anomalies and overgrowth disorders; however, efficacy data for sirolimus in patients with MCAP are lacking. Small, early-phase studies have investigated the mTOR inhibitor everolimus as a potential treatment for medically refractory epilepsy in patients with non-tuberous sclerosis cortical dysplasia [4].

The PI3Kα inhibitor alpelisib has received approval from the US Food and Drug Administration for the treatment of adult and pediatric patients 2 years of age and older with severe manifestations of PROS who require systemic therapy. Among a series of patients with severe PROS who received alpelisib under compassionate use, two patients with MCAP were described as having improvements in cognitive function, behavior, and cerebral perfusion [18]. However, data regarding their specific neurological outcomes are limited. Recently, a retrospective chart review of patients who received alpelisib for PROS as part of a managed access program ($n = 57$), termed the EPIK-P1 study, was completed [2]. The primary endpoint of EPIK-P1 was clinical response, defined as at least a 20% reduction in target lesion volume for individuals with somatic overgrowth and vascular anomalies. Overall, 37.5% of patients with complete cases ($n = 32$) treated with alpelisib met the at least 20% threshold for clinical response [2]. A total of nine patients with MCAP were enrolled in EPIK-P1, but subgroup analyses have not been reported. It is important to note that studies with alpelisib to date were not

Table 2 Ongoing clinical trials enrolling patients with *PIK3CA*-related disorders

Study title	Patient population	Description/outcomes
EPIK-P2 (NCT04589650)	Patients—initially age ≥ 6 years, with those aged 2–5 years to be enrolled later—diagnosed with PROS and a somatic *PIK3CA* mutation ($n \approx 174$)	Prospective, phase 2, multicenter study with an upfront 16-week, randomized, double-blind, placebo-controlled period, and extension periods, to assess the efficacy, safety, and pharmacokinetics of alpelisib in pediatric and adult patients with PROS
GENEPHY (NCT02890641)	Patients aged 3 months to 25 years with focal drug-resistant epilepsy, including patients with HMEG and FCD ($n \approx 450$)	Study aiming to search for brain somatic mutations in paired blood–brain samples from patients undergoing epilepsy surgery at the Rothschild Foundation, Paris
NCGENES2 (NCT03548779)	Infants and children (≤ 15 years old) referred for initial evaluation of a monogenic disorder or seen for evaluation of an undiagnosed disorder at a study-associated clinic; their parents are also eligible ($n = 806$)	Part of a consortium project investigating the clinical utility of next-generation exome sequencing. The trial will compare first-line exome sequencing to usual care and participant pre-visit preparation to no pre-visit preparation. Outcomes include number of in-patient admissions, in-patient hospital days, ER visits, specialist visits, and QoL
NCT04344626	Patients with epilepsy who are candidates for epilepsy surgery, and undergoing resective surgery for dysplastic epilepsy (e.g., FCD, HMEG, polymicrogyria) ($n \approx 150$)	Study to assess the ability of intraoperative tonometry to identify epileptogenic tissue through brain tissue stiffness measurements

Based on clinicaltrials.gov, access date May 25, 2022
ER emergency room, *FCD* focal cortical dysplasia, *HMEG* hemimegalencephaly, *PIK3CA* phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha, *PROS PIK3CA*-related overgrowth spectrum

prospective, randomized clinical trials; data regarding safety, efficacy, and pharmacokinetics of alpelisib in children with MCAP are limited. In addition, alpelisib is not thought to penetrate the blood–brain barrier, which may limit the impact on affected tissue within the CNS. A prospective study to characterize the safety, efficacy, and pharmacokinetics of alpelisib in patients with PROS disorders is underway (Table 2).

Two genetic studies (GENEPHY, NCGENES2) are enrolling patients with PROS conditions and complications such as focal drug-resistant epilepsy and brain malformations, and a trial of intraoperative tonometry in refractory epilepsy is enrolling patients with FCD, HMEG, and polymicrogyria (Table 2). However, despite these efforts, patients with MCAP continue to be underrepresented in current PROS clinical trials. Trial designs for patients with PROS disorders focus on endpoints that are dependent on lesion volume reduction for somatic overgrowth, and patients with MCAP may not have suitable evaluable target lesions. Further, many features of the disease are neurological; therefore, there is a need for clinical trials to include relevant neurologic endpoints to encourage enrollment of patients with MCAP and other PROS disorders with CNS involvement.

CONCLUSIONS

Although MCAP, HMEG, DMEG, and FCD share some of the same genetic underpinnings as other PROS conditions including Congenital Lipomatous asymmetric Overgrowth of the trunk with lymphatic, capillary, venous, and combined-type Vascular malformations, Epidermal naevi, Scoliosis/Skeletal and spinal anomalies (CLOVES), Klippel-Trenaunay syndrome (KTS), and isolated venous or lymphatic malformations, these disorders can be distinguished by brain involvement. Patients, families, and caregivers therefore face many unique challenges from the associated neurological and neurosurgical complications. Effective treatment options are limited; surgery and developmental therapies can help manage some of the manifestations but do not address the root cause of the disease. Lack of access to clinical trials of emerging targeted therapies is a challenge for patients, caregivers, and health care professionals. Further research is needed to define optimal treatment plans and identify effective therapies to treat the disease and improve patients' quality of life in this chronic and multisystem disorder.

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