**Collaborative Model for Diagnosis and Treatment of Very Rare Diseases: Experience in Spain**

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Introduction

- Mitochondrial diseases are difficult to diagnose and treat.
- Recent advances in genetic diagnostics and more effective treatment options can improve patient diagnosis and prognosis.
- However, patients with mitochondrial diseases typically experience delay in diagnosis and treatment.
- Many patients are surveyed in North America reported to seek physician advice before diagnosis.

Collaborative partnership in Spain demonstrates an effective model of networked neurology centers to efficiently diagnose and treat patients with thymidine kinase 2 (TK2) deficiency: an mitochondrial DNA depletion syndrome.

Research efforts of centers in New York City, USA and Barcelona, Spain, have established an effective partnership to identify disease models, diagnostic strategies, and treatment modalities.

Research within the Spanish collaboration investigates disease pathology and pathogenesis, leading to disease-specific diagnosis and treatment of neuromuscular disorders in the context of new molecular tools (CLAR) for Neuromuscular Diseases that specialize in mitochondrial diseases.

Objective

- To describe a unique collaboration among physicians and scientists in Spain focused on mitochondrial disorders, using diagnosis and treatment of TK2 deficiency as an example case.

TK2 Deficiency Clinical Features

- TK2 deficiency is a mitochondrial disease characterized by muscle weakness.
- Disease progression is variable, resulting in loss of ambulation, dysphagia, respiratory failure, and death in most patients, usually with early onset.
- TK2 deficiency is an ultra-rare disease with ~100 cases reported in the literature.
- TK2 deficiency was identified as an ultra-rare genetic disease (UCOS-2010) in 2010, with the first genetic description.
- Natural history studies have defined the clinical presentation phenotype.

Collaborative Care Model

- The designation of a network of national Reference Centers for Neuromuscular Disorders in Spain (CNRN) as a reference for diagnosis and treatment, has been determined to identify and hormonally treat the largest cohort of patients with TK2 deficiency worldwide.
- The Spanish collaboration resulted in diagnosis and consolidation of care for more than 30 patients with TK2 deficiency in Spain and built a network of regional neuromuscular centers (Figure 1).
- Research efforts and reference centers across regions of Spain collaborate with each other within the National Public Health System and with investigators in the U.S. to diagnose and treat patients.

Role of the Spanish Collaboration in TK2 Disease Description and Treatment

- The Spanish collaboration has facilitated a robust network of research and development over the past two decades.
- Treatment with nucleosides was pioneered by understanding of clinical presentation and the disease mechanism, resulting in the first treatment results in animal models in 2010.
- The first patient with this diagnosis was treated in 2010 in Spain.
- Between 2014 and 2015, one of the patients progressed to a very advanced stage of the disease, facilitating new investigational drug development.

Recent advances in genetic diagnostics and more effective treatment options definitely contribute to the identification and treatment of TK2 deficiency patients in Spain.

- The Spanish collaboration also facilitates differential diagnosis, patient access to disease-specific treatment modalities, and enrollment of patients into clinical studies.
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- Natural history studies have defined the clinical presentation phenotype.

Conclusion

- The Spanish experience in diagnosis and treatment of TK2 deficiency is a model for the diagnosis and development of new treatments for very rare diseases within an existing health care system.
- This collaborative model supports the development of a new therapeutic approach to progressive diseases that are difficult to diagnose and treat.
- Rapidly identifying patients with mitochondrial disorders shorten the time to diagnosis and facilitate access to treatment.

**References**


**Acknowledgments**

- No disclosures.

**Disclosures**

- All disclosures are documented in the References section.

**Supporting Information**

- Images, tables, and other supplementary materials are available at the DOI link provided in the References section.

**Figure 1. Timeline for TK2 deficiency disease description and treatment in Spain**

- The timeline illustrates the progression of TK2 deficiency diagnosis and treatment in Spain, from the identification of the disease in 2001 to the first treatment results in animal models in 2010.

- The timeline highlights the collaborative efforts of the Spanish collaboration, including the establishment of national reference centers, the development of diagnostic algorithms, and the initiation of clinical trials.

**Figure 2. Timeline for TK2 deficiency disease description and treatment in Spain**

- The timeline highlights the collaborative efforts of the Spanish collaboration, including the establishment of national reference centers, the development of diagnostic algorithms, and the initiation of clinical trials.

- Figure 2 presents the collaboration timeline for TK2 deficiency disease description and treatment in Spain, providing a visual representation of the milestones achieved through the Spanish collaboration.

**Figure 3. Role of the Spanish collaboration in streamlining mechanistic data from R&D into diagnosis and clinical care**

- The figure illustrates the role of the Spanish collaboration in streamlining mechanistic data from R&D into diagnosis and clinical care, emphasizing the collaborative efforts in advancing treatment options and patient access to care.

- The figure highlights the Spanish collaboration’s contributions to the identification and treatment of TK2 deficiency patients in Spain, showcasing the integration of research, diagnostic tools, and clinical care.

**Figure 4. Model for clinical study development**

- The model represents a framework for clinical study development, integrating research findings, diagnostic tools, and clinical care to facilitate the translation of mechanistic data from R&D into clinical practice.

- The model underscores the importance of collaboration and partnership in advancing treatment options and patient access to care.

**Figure 5. Collaboration among major reference centers across regions of Spain and research affiliates in Spain and the US**

- The figure illustrates the collaboration among major reference centers across regions of Spain and research affiliates in Spain and the US, highlighting the networked approach to diagnosis and treatment of rare diseases.

- The figure emphasizes the significance of the Spanish collaboration in facilitating a robust network of research and development, contributing to the identification and treatment of TK2 deficiency patients in Spain.

- The figure underscores the importance of international collaboration in advancing treatment options and patient access to care.