Konstantin Mechler
Dr.med.

**Orphan Drug Development in Rare Neurogenetic Disorders**

Fach/Einrichtung: Kinderheilkunde
Doktorvater: Priv.-Doz. Dr. med. Dr. rer. nat. Markus Ries MHSc (Duke Univ., USA), FCP

Orphan disorders are often chronic diseases with significant morbidity, high mortality, and lack of adequate therapies. Most of these are genetic disorders. Orphan neurogenetic disorders represent an important and research active subgroup of orphan disorders. For some of these disorders, therapies addressing the underlying cause have become available. Drug development for orphan disorders faces particular challenges, e.g., small study populations, heterogeneous phenotypes, and non-availability of animal models. Most importantly, the natural history of many orphan neurogenetic disorders is unknown.
This work was planned to contribute to current research in orphan drug development in neurogenetic disorders by answering two research questions that had not been addressed before:
1) What are key factors for successful drug development in orphan neurogenetic disorders?
2) What is the natural history of molybdenum cofactor deficiency?

For research question 1, key factors for successful drug development were investigated in lysosomal storage disorders by means of a comprehensive analysis of orphan drug designations and approvals based on data provided by the FDA. Lysosomal storage disorders are a very research active subgroup of orphan disorders. Since the introduction of the US Orphan Drug Act in 1983 until 2013, 14 orphan drugs, mostly enzyme replacement therapies, were developed for lysosomal storage disorders. Statistically significant key factors for an orphan drug approval respective designation were a disease prevalence of $\geq$ 5/1,000,000, the non-requirement of a primary neurological endpoint, and the existence of a regulatory precedent (statistically significant only for orphan drug designation). Additionally, enzyme replacement therapies were the most common technology platform used.

For research question 2, the yet undefined natural history of the orphan neurogenetic disorder molybdenum cofactor deficiency was quantitatively analyzed based on a systematic literature review of all published cases (n=82). Molybdenum cofactor deficiency type A is of particular interest because an experimental treatment with substrate replacement has been successfully performed in single cases. The median survival for the overall untreated population was 36 months. Initial cardinal disease features at onset were seizures (72%) as well as feeding difficulties (26%), hypotonia (11%), developmental delay (9%), hemiplegia (2%), lens dislocation (2%), and hyperreflexia (1%) were reported. The median age of onset of the disease was on the first day of life, the median age at diagnosis was 4.5 months. The median time to diagnosis (diagnostic delay) was 89 days.
Molybdenum cofactor deficiency has its onset in the neonatal period and infancy. There is considerable diagnostic delay. Although seizures were the most frequent initial cardinal sign, molybdenum cofactor deficiency should be considered as a differential diagnosis in patients presenting with hypotonia, developmental delay, or feeding difficulties. S-sulphocysteine analysis should be routinely used when molybdenum cofactor deficiency is suspected. In neuroradiological exams more than 40% of patients had signs of reduced myelination, enlarged ventricles, cerebral atrophy, and cystic lesions. The survival data will inform further natural history and therapeutic studies which are important next steps in the process of an orphan drug development in molybdenum cofactor deficiency.

The published data of the present work are of relevance for patients, physicians, researchers, pharmaceutical companies, and regulatory agencies involved in orphan drug development for neurogenetic disorders.