Critical evaluation of Newborn Screening on the metabolic disease course in cytosolic Urea Cycle Disorders

Zielonka M, Köller S, Scharre S, Seidl M, Köller S, Gleich F, Probst I, Druck AC, Nagamani SCS, Gropman AL, Hoffmann GF, Garbade SF, Posset R; for the Urea Cycle Disorders Consortium (UCDC) and European registry and network for Intoxication type Metabolic Diseases (E-IMD) Consortia Study Group*

Introduction: The implementation of newborn screening (NBS) programs for the cytosolic urea cycle disorders (UCDs) citrullinemia type 1 (CTLN1) and argininosuccinic aciduria (ASA) is subject to controversial debate. The aim of this study was to assess the impact of NBS on the metabolic disease course of affected individuals in a severity-adjusted manner.

Method: In 115 individuals with CTLN1 and ASA, we compared the severity of the initial hyperammonemic episode (HAE) and the frequency of (subsequent) HAEs with the mode of diagnosis. Based on a recently established functional disease prediction model1, individuals were stratified according to their predicted severe or attenuated phenotype.

Results: NBS predominantly identified individuals with an attenuated phenotype of CTLN1 and ASA (Fig. 1). Early identification by NBS enabled an efficient reduction of the severity of the initial HAE independent of the underlying phenotype (Fig. 2A, B), but was not associated with a reduced number of subsequent HAEs for both severe and attenuated phenotypes (Fig. 3A, B).

Conclusion: The use of a functional disease prediction model enabled the severity-adjusted evaluation of a diagnostic intervention (such as NBS) on the metabolic disease course in UCDs, which is of importance to avoid overestimation of the NBS effect. Future long-term studies will need to evaluate the clinical impact of this finding, especially with regard to mortality, as well as cognitive outcome and quality of life of survivors. We propose to use comparable severity-adjusted stratification methods to assess the impact of NBS for further inherited metabolic diseases in the future.


Figure 1: Mosaic plot of the association of diagnostic mode with phenotypic severity in 115 individuals with CTLN1 and ASA. A) Fourfold table showing the proportion of individuals with a specific phenotypic severity (i.e. predicted severe or attenuated) with a higher proportion of individuals identified by newborn screening (n=71.2%). Individuals with predicted attenuated forms of CTLN1 and ASA are overrepresented in the NBS group. B) The height of the bars in a row represents the proportion of individuals with a specific phenotypic severity (i.e. predicted severe or attenuated). The width of the bars in a row represent the proportion of individuals identified by newborn screening in comparison to the expected (1/2). C) The intensity of color reflects the discrepancies between observed and expected frequencies. Red color shows that observed frequencies are higher than expected, and blue color shows that observed frequencies are lower than expected.

Figure 2: Newborn screening is associated with an attenuated initial hyperammonemic decompensation in individuals with CTLN1 and ASA. A) Boxplot illustrating peak plasma NH₃ [μmol/l] at initial decompensation for individuals with a predicted severe phenotype identified by newborn screening (n=6) or SK (n=18). Data are shown as median (black thick line) and mean (triangle), length of the box corresponds to the interquartile range (IQR), upper and lower whiskers correspond to max 1.5×IQR, each point represents an outlier. Welch Two Sample t-test, p=0.001. B) Boxplot depicting peak plasma NH₃ [μmol/l] at initial decompensation for individuals with a predicted attenuated phenotype identified by newborn screening (n=12) or SK (n=18). Data are shown in analogy to Fig. 2A. Welch Two Sample t-test, p=0.060. SK, selective metabolic testing after the manifestation of first symptoms.

Figure 3: Newborn screening is not associated with a reduced number of HAEs in individuals with CTLN1 and ASA. A) Boxplot illustrating number of hyperammonemic events per year of observation for individuals with a predicted severe phenotype identified by newborn screening (n=6) or SK (n=18). Data are shown as median (black thick line) and mean (triangle), length of the box corresponds to the interquartile range (IQR), upper and lower whiskers correspond to max 1.5×IQR, each point represents an outlier. Welch Two Sample t-test, p=0.531. B) Boxplot depicting number of hyperammonemic events per year of observation for individuals with a predicted attenuated phenotype identified by newborn screening (n=12) or SK (n=18). Data are shown in analogy to Fig. 3A. Welch Two Sample t-test, p=0.536. SK, selective metabolic testing after the manifestation of first symptoms.

Literature: