Newborn Screening Pilot Study on Urea Cycle Disorders and Proposal for a Screening Algorithm

German: Pilotstudie zu Harnstoffzyklusstörungen und Vorschlag eines Screening-Algorithmus

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Objective: To evaluate feasibility, diagnostic and process qualities, as well as clinical benefit of newborn screening (NBS) for urea cycle disorders (UCDs). **Methods:** Between 2016 and 2023, 624,480 neonates were enrolled in the German NBS pilot study including NBS for UCDs by tandem mass spectrometry. In addition, confirmed cases were enrolled in an observational, multi-centre outcome study assessing clinical and neurodevelopmental outcomes. **Results:** NBS for UCDs demonstrated high sensitivity (100%) and specificity (99.988%) with a positive predictive value (PPV) of 0.2. Nineteen cases (seven ornithine transcarbamoylase deficiency, seven argininosuccinate synthetase 1 deficiency, four argininosuccinate lyase deficiency, one carbamoylphosphate synthetase 1 deficiency) were confirmed, yielding a cumulative birth prevalence of 1:32,867 newborns. Despite short process times, more than 50% of screened individuals with a UCD were already symptomatic at first NBS report. Retrospective analyses indicated that integration of metabolite ratios (e.g., ornithine/citrulline) may further enhance PPV. Outcome data from 25 individuals revealed higher rates of metabolic decompensations and hospitalizations in mitochondrial UCDs versus cytosolic forms. At last follow-up, 55% showed disease-related symptoms, and mean IQ was reduced in symptomatic individuals, but mortality was lower than previously reported. **Conclusion:** NBS for UCDs is technically feasible and enables early diagnosis. While early-onset decompensations remain difficult to prevent, screening reduces mortality. Refinement of the screening algorithm may further improve specificity and clinical benefit.