Long-term clinical outcomes of patients with VLCAD deficiency identified by newborn screening

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Introduction

Very long-chain acyl-CoA dehydrogenase deficiency (VLCADD) is an autosomal recessive disorder of mitochondrial long-chain fatty acid metabolism resulting in a variable clinical phenotype. VLCADD is a target disease of newborn screening (NBS) programs worldwide, but data on long-term outcome are scarce. This study aims to evaluate clinical outcomes of screened individuals with VLCADD.

Methods

A national, multicenter, observational study of children and adolescents with VLCADD identified by NBS between 1998 and 2025 was conducted. Data collection included NBS results and confirmatory diagnostics, medical history, clinical manifestation, metabolic decompensations, therapeutic measures and cognitive testing. Individuals were stratified into groups (attenuated(a)/classic (c)VLCADD) according to disease severity (i. e. residual enzyme activity ≤10%/>10%).

Results

In total, 108 screened individuals with VLCADD (46 aVLCADD, 62 cVLCADD) were included. Until last follow up at median 8.0 years of age, 73% (N=78) became symptomatic or experienced at least one metabolic decompensation (46%, N=49), 27% (N=29) already neonatally. Two infants, both with cVLCADD, died due to severe cardiomyopathy, neonatally (day 2) and at the age of 8 years (cVLCADD mortality: 3.2%), respectively. As expected, clinical phenotype differed between aVLCADD and cVLCADD in occurrence of symptoms [myopathy (35% vs.71%, $p<0.001$), hepatopathy (28% vs. 36%, $p=0.394$), manifest rhabdomyolysis (7% vs. 49%, $p<0.001$), hypoglycemia (9% vs.25%, $p=0.033$) and cardiomyopathy (2% vs. 20%, $p=0.006$)] as well as the manifestation (17% vs. 67%, $p<0.001$) and frequency of (recurrent) metabolic decompensations (e. g. hypoglycemia or rhabdomyolysis). No metabolic decompensations were reported in patients with a residual enzyme activity above 18%.

Conclusion

NBS enables early diagnosis and treatment. Mortality in the screened cohort was lower than the previously reported mortality for unscreened VLCADD cohorts (up to 75%). However, NBS and early treatment cannot prevent metabolic decompensations in all patients, particularly not in those with cVLCADD. The residual enzyme activity and thus the disease severity are important prognostic markers.