

Developmental Medicine & Child Neurology 2017, 59: 776–785
doi: 10.1111/dmcn.13472

Commentary on

Disease Natural History and Phenotypic Profiles in a Cohort of Patients Affected with variant Late Infantile Ceroid Lipofuscinosis 5 (CLN5)

Simonati et al. 2017 Developmental Medicine & Child Neurology, 59: 815–821

The value of a comprehensive natural history for rare diseases

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This manuscript [1] describes the natural history of 15 children with late infantile CLN5 disease, that is, disease caused by mutations in *CLN5* that begins between the ages of 2-7 yrs. This gene encodes a soluble lysosomal protein of unknown function, and is one of more than a dozen genes that cause diseases collectively known as the neuronal ceroid lipofuscinoses or Batten disease. Alongside the natural history, including some neurophysiology, the pathology and mutations in all patients were determined and expression of mutant protein was characterised for some, confirming absence of expressed protein as expected for some mutations.

The first published description of CLN5 disease was in 1991 in Finnish patients [2], with the gene linked to chromosome 13 a few years later and then identified in 1998. These children were carrying the same mutation and therefore had a rather homogenous disease course. This study is therefore of interest and value because it (1) provides a more detailed natural history of late infantile CLN5 disease than previously available including survival data, bringing the total number of patients described in the literature to 40, (2) develops a new rating scale that could be used internationally to further extend this natural history data, (3) describes disease in patients with different mutations (nine different mutations in total) and nationalities, allowing genotype, phenotype correlation, and (4) demonstrates the value of collaborative disease registries for rare diseases, as some of these patients are contained within one such international registry launched approximately 5 year ago through an EU FP7 project DEM-CHILD that has since expanded to include other countries.

The specially devised rating scale periodically assesses changes in six functional domains over time, allowing the disease course to be established for each patient. The overall findings are significant because the presenting symptom and disease progression is not identical across all patients. For example, a decline in language abilities was the presenting symptom in less than half the patients. This study, nevertheless, clarifies that an early feature is impairment in language and learning, with onset of seizures and loss of vision being late occurrences. This is in contrast to other types of NCLs that begin in late infancy. Disease rating scales have long been used for the NCLs, the first in 2002 for classic late infantile CLN2 disease [3], and later ones developed for CLN3 disease [4]. This rating scale could readily be adapted for the whole group of variant late infantile NCLs – CLN6, CLN7 and CLN8 diseases. This scale may also be useful for those carrying particularly mild mutations in CLN5, causing later onset of disease that may be much more protracted [5].

The most interesting and perhaps unexpected finding of this study is that all the children progressed similarly from the onset with a moderate progression for the first 3 years. However, after 3 years, the rate of decline varied and this correlates with the genotype. Thus, use of a rating scale in CLN5

disease can detect changes in the rate of decline from the 'typical' disease arising from complete loss of CLN5 function. This is important as it allows families and supporting agencies for health, social care and education, to plan future care for these children based on genotype and the associated predicted or emerging disease course, including life expectancy which for some patients may extend into their twenties.

This data further provides the detailed natural history that is required as the basis of a control cohort in clinical trials. Thus, this will be an essential and invaluable resource as trial therapies emerge for CLN5 disease, to assess the efficacy of clinical trials. For this particular disease, these are likely to be based on enzyme replacement therapy, either direct, for one currently under development for CLN2 disease, or indirect via gene therapy. These therapies must be delivered as early in the disease course as possible to be most effective. For CLN5 disease, this will ideally be in the pre-symptomatic phase or as early in the initial 3-year slowly progressing phase as possible. For other NCLs with an earlier and more rapid deterioration, the therapeutic window is much shorter.

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