PREVALENCE OF SANFILIPPO SYNDROME AND SUB-TYPES IN MAJOR GEOGRAPHICAL REGIONS

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Introduction:

Mucopolysaccharidosis-III, also known as MPS-III or Sanfilippo syndrome, is one of a number of Mucopolysaccharidoses (MPS) - a group of rare genetic disorders caused by deficiencies of lysosomal enzymes. These are in-born errors of metabolism, and are autosomal recessive genetic disorders. MPS-III consists of 4 distinct sub-types each linked with a different enzyme deficiency as follows:

- MPS-IIIA - 17q25.3 (sulphamidase deficient)
- MPS-IIIB - 17q21 (N-Acetylglucosaminidase deficient)
- MPS-IIIC - Chromosome 14 (Acetyl-CoA:alpha-glucosaminide-acetyltransferase deficient)
- MPS-IIID - 12q14 (N-acetylglucosamine 6-sulphatase deficient)

Patients tend to appear normal at birth, with symptoms emerging after ~2 years of age. Signs and symptoms vary according to disease severity and age of onset of symptoms but can include: decline in learning ability (typically occurs between 2-6 years of age), child may have normal growth during the first few years but final height is below average, delayed development followed by worsening mental status, behavioural problems, coarse facial features, diarrhoea, full lips, heavy eyebrows that meet in the middle of the face above the nose, sleep difficulties, stiff joints that may not extend fully, and walking problems. It is a progressive condition eventually leading to premature death. Patients tend not to live beyond the 2nd or 3rd decade of life, with the average life-span for patients being between 15-20 years.

There are currently no treatments available for MPS-III, unlike other forms of MPS where enzyme replacement therapy has been shown to be effective in treating the underlying disease and thus alleviating symptoms and extending life-expectancy. In part this is due to the diverse nature of MPS-III and the requirement for 4 different treatments. Little is known regarding the prevalence of MPS-III and the frequency of the different sub-types in different geographic locations.

Methods:

A systematic search and review of published literature (including Medline, Embase, Cochrane CENTRAL) reporting the birth prevalence and natural history of MPS-III was conducted, with a focus on collating data from observational studies. Additional searches were conducted for “lysosomal storage disorders” and “mucopolysaccharidoses”. Papers were selected for inclusion in the analysis based on sample size and method of selection, diagnostic criteria and genetic origin of the sample in the study. A further literature search was conducted to find published data regarding sub-type within an MPS-III cohort of patients in each region and country within the study. Forty five papers were identified (from a total of 588 papers) for inclusion in the analysis and evaluated according to the MOOSE criteria.

Incidence rates for MPS-III in the birth cohort were available for a number of countries, although prevalence data are scarce. Estimated prevalent caseload was been modelled based on average life-expectancy of individuals with MPS-III (by sub-type) coupled with number of cases expected in live births per year (birth prevalence). There is no effective treatment for MPS-III, thus birth rate and survival were kept constant throughout the analysis. Rates were assumed to be roughly equivalent between males and females since this is not an X-linked condition and therefore equally likely to occur in females as in males.

Data from the United Nations World Populations Prospects database (2018) for each country in the study, split by gender and 5-year age cohort were used as the basis for calculating birth prevalence caseload and estimating overall survival and thus total prevalent caseload with MPS-III in each country.

Countries studied included: USA, Canada, Brazil, Australia, Japan, China, India, Turkey and 14 EU countries.

Results:

Frequency of both MPS-III and its sub-types vary by region. Where no country specific sub-type breakdown was available, pooled analysis for similar genetic populations has been applied. Birth-cohort rates sourced and applied directly for the majority of countries. Exceptions as follows: Brazil - no known incidence, however the Brazilian MPS network provides good data on diagnosed patients; China & Japan are modelled from data for Taiwan; Spain - currently based on data for Portugal; Italy - currently based on data for Greece, Turkey - top-line modelled using Greece, but local data available for subtypes; Russia - modelled based on average for Eastern EU. Overall, we calculated a total of ~7,000 patients with MPS-III of which approximately 34% were sub-type A, 60% sub-type B, 5% sub-type C and <1% sub-type D.

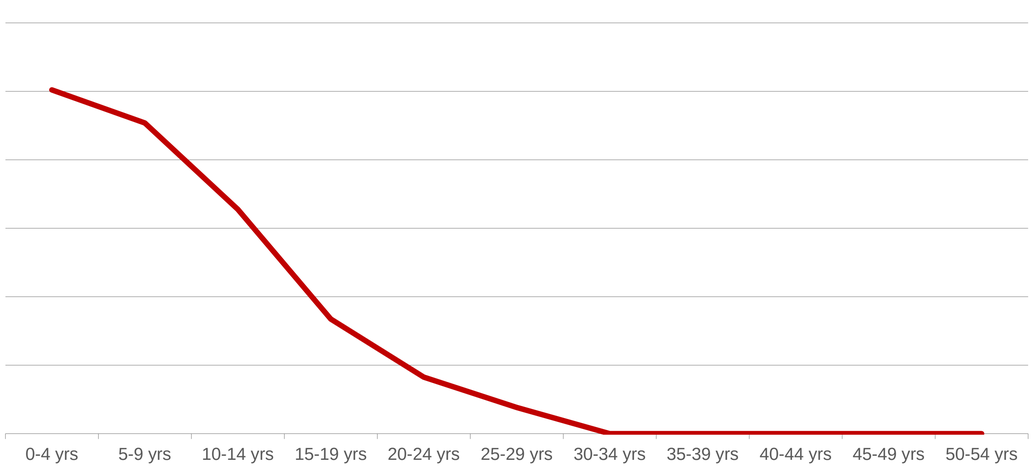

Figure 1: % Prevalence of MPS-III by Age

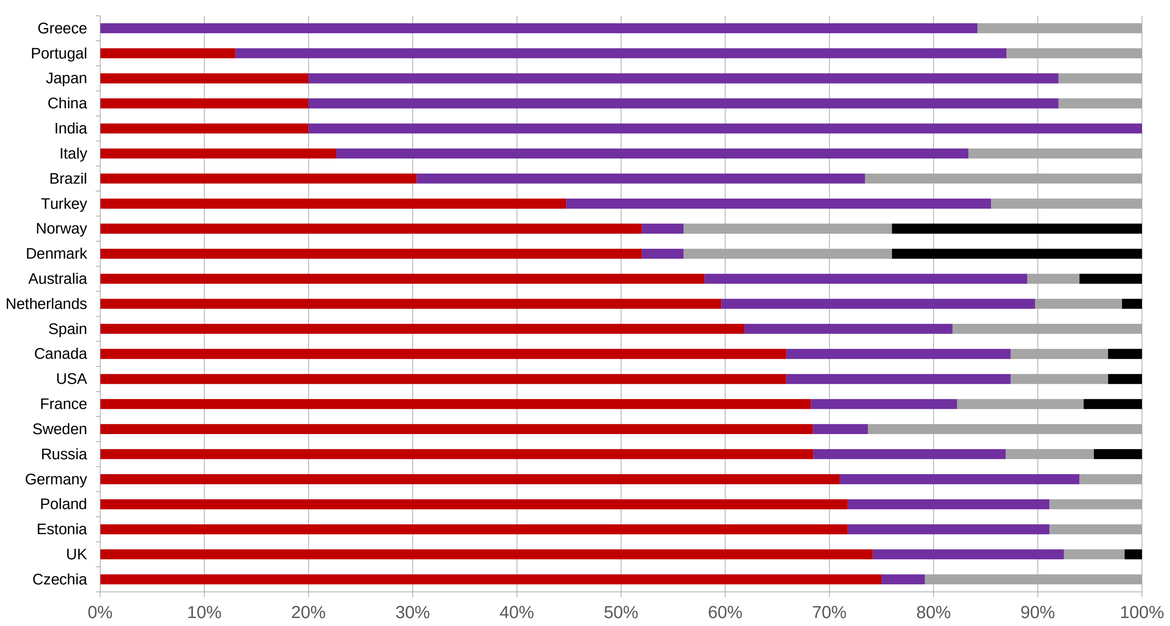

Figure 2: Frequency of MPS-III Sub-type by Country

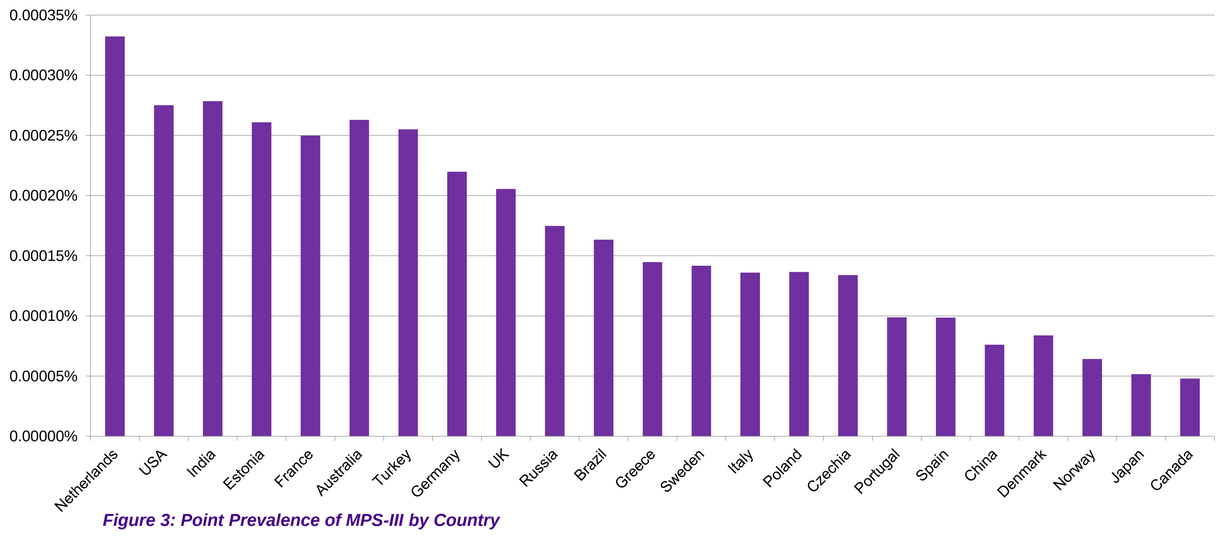

Figure 3: Point Prevalence of MPS-III by Country

Figure 4: Total Patient Burden of MPS-III by Sub-type (all countries)

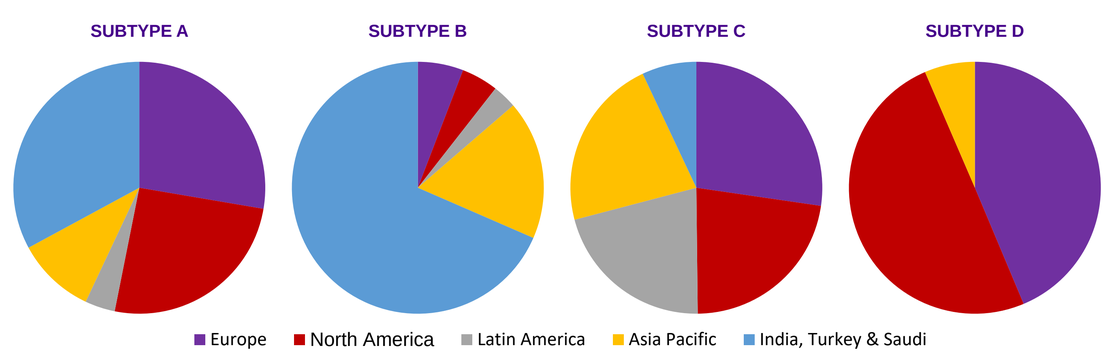

Figure 5: Distribution of MPS-III Sub-types by Region

Conclusions:

Prevalence of MPS-III is rare. According to the available published literature, there is a marked difference in both the frequency of MPS-III by country and region, but also a difference in the sub-type form present. Notably, Norway and Denmark have a far higher proportion of MPS-IIID in their patient cohorts than any other Northern EU country, which may suggest a founder-effect. Greece, by contrast appears to have no MPS-IIIA. While MPS-IIIB appears to contribute the highest patient burden, this is mainly because of the contribution of India to the overall calculations. Furthermore, detection of the sub-types can not be performed in an equivalent and consistent manner due to a lack of identification of the mutation that causes MPS-IIIC. Birth prevalence estimates are lacking in some significant geographic areas (e.g. China / Japan), even though there are patient registries (e.g. Brazil) available suggesting that the disease is present and diagnosed

The variation in the occurrence of the sub-types of MPS-III has clear implications for development of treatments for this condition. While MPS-IIIB appears to contribute the highest number of patients, the majority of these reside in India where access to healthcare may present a challenge. Within Northern America and Europe, MPS-IIIA has the highest burden.

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