Carriers of Haemophilia B Leyden: Factor IX levels during life

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Introduction: Haemophilia B Leyden is a relatively rare disease caused by mutations in the promotor region of the F9 gene. Patients are characterized by low Factor IX (FIX) levels during childhood, but during puberty FIX levels rise 4-5% per year. Although this rise gradually levels off, adult patients usually have enough FIX for normal haemostasis.[1] Due to lionization, some carriers have factor IX levels in the same range as affected men. Little is known about the course of factor IX levels in carriers. **In this retrospective chart review we tried to clarify the relation between age and FIX levels in carriers of Haemophilia B Leyden** .

Study population/Methods: Pedigrees of a relatively large Haemophilia B Leyden population registered at the Haemophilia Treatment Centre Groningen were explored. For all obligate and/or DNA proven carriers, medical records were reviewed to find known FIX measurements. We identified 37 obligate and/or proven carriers, 20 of whom had retrospective FIX levels available. All FIX levels were measured by one-stage clotting assay, without changes over time. **After exclusion of measurements before 1 year of age or during supplementation or pregnancy, 35 FIX levels of 18 different carriers were left: for 9 carriers only one FIX measurement was available and for the other 9 carriers two or more measurements were available.**

The carrier cohort was divided in two groups: before and after puberty. **Five carriers were measured before puberty (< 12 years of age), 14 carriers were measured after puberty (≥ 16 years)**. If a carrier had measurements available before and after puberty (one case) only measurements before puberty were used. Only one carrier had a measurement available during puberty, which could not be used for analysis. When multiple measurements were available for one carrier the mean was taken.
Five carriers had measurements during and outside pregnancy.

Results:

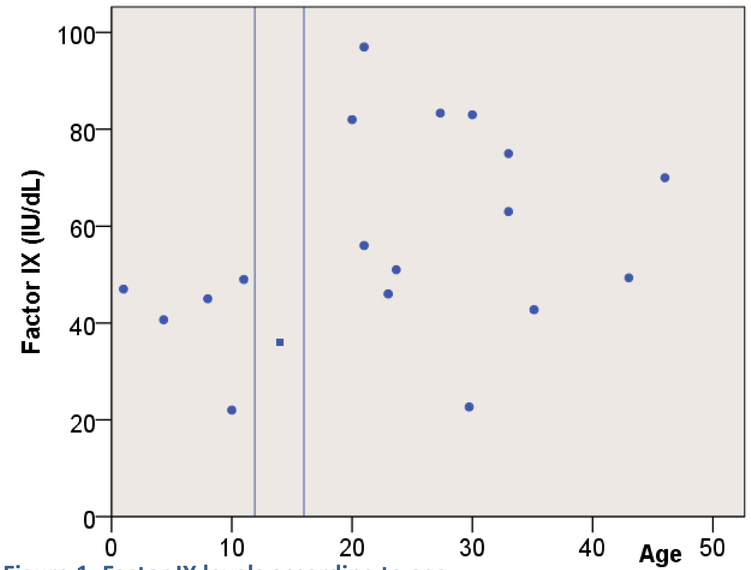

Figure 1: Factor IX levels according to age
● Each point represents a FIX measurement or the mean of several FIX measurements for one independent individual.
■ One individual had a measurement during puberty available.

The overall pattern shows a rise of factor IX levels with age, but the course of individuals differed a lot. Difference between age groups < 12 years and ≥ 16 years is significant (p=0.038) (t-test).
Mean (SD) < 12 years = 41 IU/L (11) and ≥ 16 years = 63 IU/L (21).

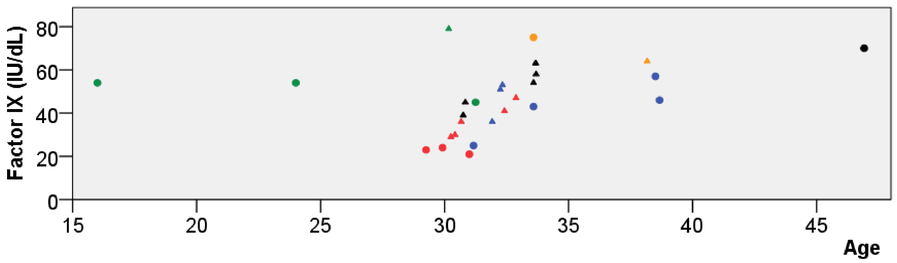

Figure 2: Factor IX levels during and outside pregnancy in the five available cases
● Measurement outside pregnancy ▲ Measurement during pregnancy. Each colour represents one carrier.

Conclusions: On an individual level the course of FIX levels in Haemophilia B Leyden is variable. On a group level, FIX levels seem to be higher after puberty than before puberty. Whether this rise is a reflection of the physiologic rise seen in the healthy population, or specific for Haemophilia B Leyden remains unanswered. Since Kurachi et al.[2] reported the rise in affected men to be caused by grotwh hormone (instead of the earlier proposed androgens), both seem to be possible.

Our results show it is usefull to measure FIX levels several times during life, since individual courses differ. The rise observed on group level in FIX levels is clinical relevant because it could have consequences for treatment of Haemophilia B Leyden carriers.
In the five reported cases, **FIX levels seem to rise during pregnancy**. **More research on this topic has to be done**, since a rise in FIX levels during pregnancy could have consequences for supplementation before delivery.

Limitations of this study are the small sample size and the retrospective design, with variable amounts of measurements and timeintervals between measurements. However, given the rarity of disease, this is as far as we know the largest collection of carriers with Haemophilia B Leyden. We would invite everyone to collect FIX measurements before and after puberty to obtain more knowledge about the course of FIX levels and improve treatment.

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