Epidemiology of Neurofibromatosis Type 1 in Finland: Incidence, Mortality, Pregnancies and Congenital Malformations

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Jussi Leppävirta, MD, Specialist in Dermatology and Allergology, University of Turku and Turku University Hospital, Turku, Finland, defended his PhD thesis on June 1st, 2018. The opponent was Associate Professor Hannele Laivuori from University of Tampere, and custos was Professor Veli-Matti Kähäri University of Turku, Finland. The thesis was supervised by Dr. Sirkku Peltonen and Professor Juha Peltonen. The thesis can be found in: http://urn.fi/URN:ISBN:978-951-29-7261-6

Neurofibromatosis type 1 (NF1) is a dominantly inherited cancer syndrome, which is caused by mutations in the NF1 gene. Because of the high mutation rate of the gene, approximately half of the patients have a new mutation, while none of the parents have the disorder. The incidence of NF1 is estimated to be approximately 1:3,000. The best-known symptoms of NF1 are neurofibromas on the skin, but NF1 is a multisystem disorder associated with a decreased overall survival and increased risk for pathologies such as cancer, learning difficulties, epilepsy and speech defects.

While there are some previous epidemiological studies on NF1-associated pregnancies and mortality of NF1, data is very limited. No epidemiological data is reported on birth size or overall risk for congenital malformations in NF1. We have acquired a nationwide cohort of approximately 1,500 patients with a confirmed diagnosis for NF1, and 10 matched controls per NF1 patient were collected. The data was linked with administrative registers to study incidence, mortality, pregnancies, birth size and congenital malformations of NF1.

We observed that the incidence of NF1 in Finland was approximately 1:2,000, which is higher than previously generally accepted. Mortality of NF1 was considerably higher than in the general population. Pregnancy duration was shortened by a fetus with NF1, and the risk for several pregnancy and delivery complications was increased among NF1 mothers. Birth weight was decreased by having a mother with NF1, while having NF1 present in the child increased it. The risk for congenital malformations was almost three-fold among NF1 children compared to matched controls.

Our study highlights a wide spectrum of ailments that NF1 causes, and the results can be utilized when guidelines of treatment and follow-up of NF1 are developed.

Fig. 1. Jussi Leppävirta defeneded his PhD thesis on June 1st, 2018.

The following main conclusions can be drawn on the basis of this study:

- The incidence of NF1 is approximately 1:2,000, which is higher than previously generally accepted. The incidence of NF2 was in line with previous studies being approximately 1:39,000 in our study. (I)
- NF1 increases mortality significantly. Especially, mortality among NF1 females aged less than 50 is considerably higher than in the general population. (I)
- NF1 of the fetus slightly shortens pregnancy duration. While the shortening is clinically insignificant, it is noteworthy because only little is known about the role that the fetus plays on the timing of the delivery. (II)

- Cesarean section, hypertension during pregnancy/preeclampsia, oligohydramnios, placental abruption, poor fetal growth and maternal care for disproportion were significantly more common among mothers with NF1 than in controls. (II)
- NF1 of the mother decreases birth weight, while NF1 of the fetus increases it. Head circumference at birth is increased by NF1 of the fetus but is not significantly affected by NF1 of the mother. (III)
- The frequency of congenital malformations is increased among NF1 children. Congenital malformations are increased in cardiovascular, musculoskeletal and urinary systems. Also risk for malformations in the group of eye, ear, head and neck was increased. (IV)

List of original publications

1. Uusitalo E, Leppävirta J, Koffert A, Suominen S, Vahtera J, Vahlberg T, et al. Incidence and mortality of neurofibromatosis: a total population study in Finland. J Invest Dermatol 2015; 135: 904.
2. Leppävirta J, Kallionpää RA, Uusitalo E, Vahlberg T, Pöyhönen M, Timonen S, et al. The pregnancy in neurofibromatosis 1: A retrospective register-based total population study. A J Med Genetics Part A, 2017, 173(10), 2641- 2648.
3. Leppävirta J, Kallionpää RA, Uusitalo E, Vahlberg T, Pöyhönen M, Peltonen J, Peltonen S. Neurofibromatosis type 1 of the child increases birth weight. (submitted manuscript)
4. Leppävirta J, Kallionpää RA, Uusitalo E, Vahlberg T, Pöyhönen M, Peltonen J, Peltonen S. Congenital anomalies in neurofibromatosis 1: a retrospective register-based total population study. Orphanet J Rare Dis 2018; 13(5).