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High Rate of Twins among Offspring of Mothers with the Järvi-Hakola-Nasu Disease and with Comments on Disorders Associated with Twinning

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Abstract. Finnish mothers with Järvi-Hakola-Nasu disease, progressive dementia with lipomembranous polycystic osteodysplasia (McKusick 221770) have a high rate of twin maternities, 128.2/1000. The exact 99% confidence intervals are 28.7 – 322.2/1000, thus above the average twinning rate in Finland, i.e. 15/1000. This eightfold increase in twinning may be an indication of a disturbed cortico-hypothalmic-hypophyseal axis or an other premorbid hormonal imbalance. It is concluded that even if dizygotic twinning is as a rule an event in itself, not only iatrogenic factors, as ovulation inducers, etc., but also some genetic disorders may be associated with twinning. More studies are needed to elucidate the incidence of twinning in families with these disorders.

Key words: Twinning rate, Finland, Nasu-Hakola disease, Brain-bone-fat disease, Polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy, Pre-senile progressive dementia, Associations with twinning

INTRODUCTION

Järvi-Hakola-Nasu disease (JHND), polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy or membranous lipodystrophy with progressive dementia (McKusick 221770) is a rare autosomal recessive disease of brain, bones and fat tissue. So far 130 cases have been diagnosed, most of them in Japan, Finland and other Nordic countries [1, 4, 18-23, 29, 36]. The disease causes progressive presenile dementia and its course is fatal. Mean life time is about 40 years [18-19]. The intellectual deterioration and the change of personality in patients with the JHND begin usually not until at fourth decade and so these patients have time to get children.

MATERIAL AND METHODS

We have gathered information of family constitutions of the probands from the local registry offices for genealogical studies in local parish archives in Finland. Miscarriages reported by probands but not registered in the archives have not been considered.

RESULTS

Of 22 Finnish patients 21 had been married, one of them twice, and they had together 61 children, of which the 14 mothers with JHND had 39 maternities with 5 sets of twins (Fig. 1-3) i.e. a twinning rate of 128.2/1000 (Table 1). The 7 married males with JHND had 17 singleton children but no twins. In the sibships of the 22 patients (Table 2) with JHN the twinning rate 19.6/1000 was not significantly increased.

DISCUSSION

The twinning rate varies in different populations. Far East populations have low twinning rates (about 5/1000). Even if no less than one-fourth of the genetic characteristics of the Finns of today is of non-European origin, that is primarily of Eastern origin [30], the twinning rates in Finland – as in other Northern countries – have been high, 14-15/1000.

Fig. 1

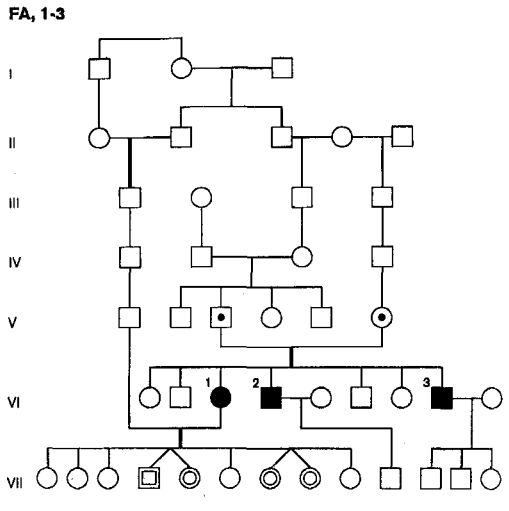

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Fig. 2

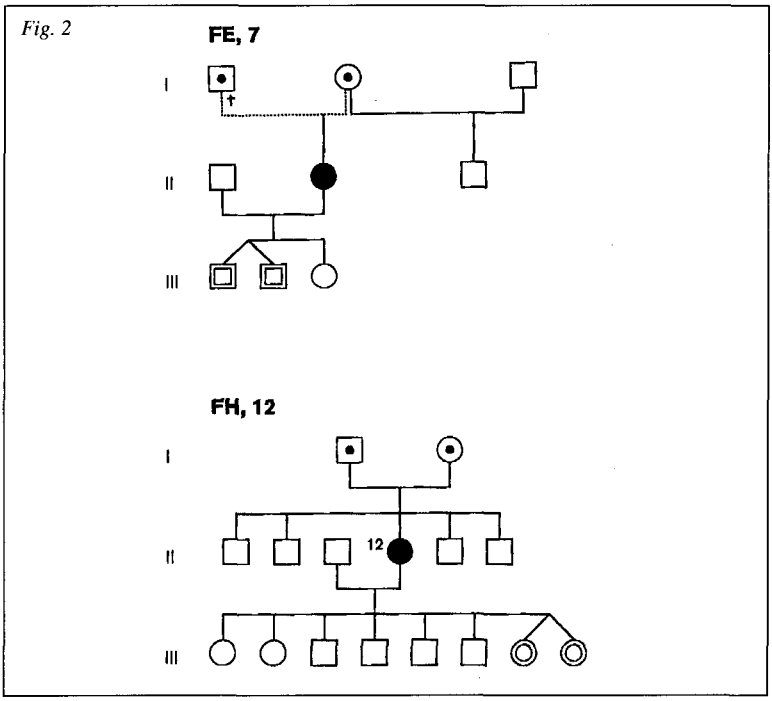

Fig. 3

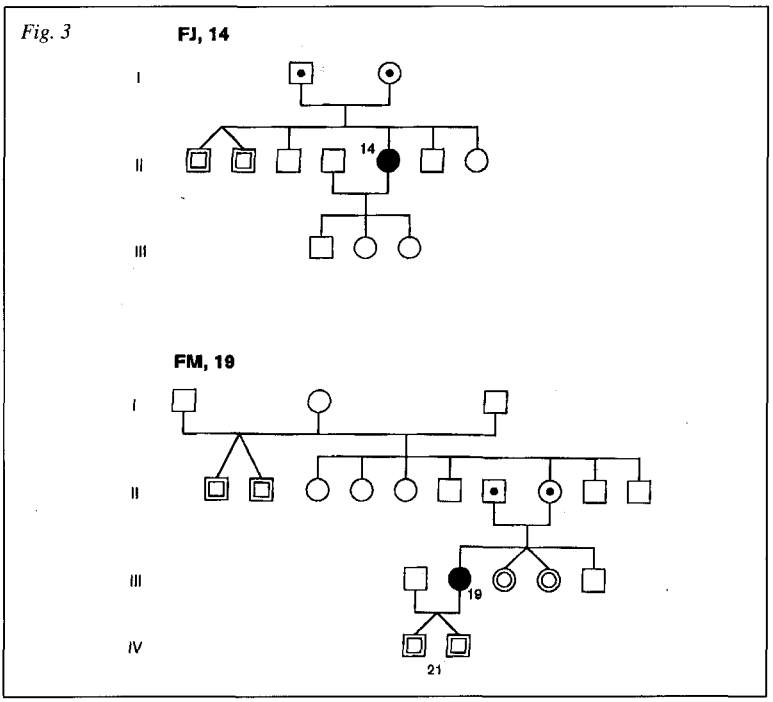

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Table 1 - Twins among offspring of Finnish patients with Nasu-Hakola disease

Pedigree and index case	Maternities							
	Singleton			Twin sets				
	M	F	Total	MM	MF	FF	Total	Total
A 1 Female		5	5		1	1	2	7
A 2 Male	1		1					1
A 3 Male	2	1	3					3
B 4 Male		4	4					4
C 5 Female	1	1	2					2
D 6 Male	1	1	2					2
E 7 Female		1	1	1			1	2
F 8 Female	1		1					1
G 9 Female	1	1	2					2
G 10 Female	2		2					2
G 11 Female	1	2	3					3
H 12 Female	4	2	6			1	1	7
I 13 Male								0
J 14 Female	1	2	3					3
K 15 Female	1	1	2					2
K 16 Male	1		1					1
K 17 Female	2	3	5					5
L 18 Male	2	1	3					3
M 19 Female				1				1
N 20 Male	2	1	3					3
O 21 Female	2		2					2
P 22 Male								0
	25	26	51	2	1	2	5	56
Male index	9	8	17	0	0	0	0	17
Female index	16	18	34	2	1	2	5	39

Twinning rate among offspring of patients = 89.3/1000

CI = 29.6–196.2. $p<0.05$; CI = 19.8–232.7. $p<0.01$

Twinning rate among offspring of female patients = 128.2/1000

CI = 43.0–274.3. $p<0.05$; CI = 28.7–322.2 $p<0.01$

In general population of Finland a twinning rate of about 15/1000 would be expected. This value is well outside the above mentioned confidence intervals (CI). Thus the discrepancy can be considered significant ($p<0.01$).

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Table 2 - Twinning in sibships of Finnish patients with Nasu-Hakola disease, NHD (index cases excluded)

Pedigree and index case	Maternities				
	Singleton				
	M	F	Total	Twin sets	Total
A 1 Female	4	2	6	–	6
A 2 Male	3	3	6	–	6
A 3 Male	3	3	6	–	6
B 4 Male	1	3	4	–	4
C 5 Female	–	–	0	–	0
D 6 Male	2	6	8	–	8
E 7 Female	1	–	1 [a]	–	1
F 8 Female	2	2	4	–	4
G 9 Female	2	7	10 [b]	–	10
G 10 Female	2	7	10 [b]	–	10
G 11 Female	2	7	10 [b]	–	10
H 12 Female	4	–	4	–	4
I 13 Male	10	5	15 [c]	–	15
J 14 Female	2	2	4	1MM	5
K 15 Female	1	1	2	–	–
K 16 Male	–	2	2	–	2
K 17 Female	–	4	4	–	4
L 18 Male	1	–	1	–	1
M 19 Female	1	–	1	1FF	2
N 20 Male	1	2	3	–	3
O 21 Female	1	–	1	–	1
P 22 Male	1	2	3	–	3
	44	58	105	2	107 [d]
Male index case	22	26	48	0	48
Female index	25	32	57	2	59

Twinning rate in sibships of patients with NHD = 2/107 = 19.6/1000

Twinning rate in sibships of female patients with NHD = 2/59 = 33.9/1000

a) Half-sib (common mother)

b) 1 sib stillborn, sex unknown

c) All of them half-sibs (common mother) to the index case

d) Included 16 half-sibs. None of them were twins

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During 1750-1949 in the isolated archipelago Åland and Åboland (Turunmaa) in south-western Finland the highest twinning rate among whites (around 20/1000) has been found [10-13]. During 1960-1969 in the counties of Mikkeli and Kuopio in the native area of most JHND patients, they were 15.4. and 16.3/1000, respectively [3]. The incidence of twin maternities among mothers with JHND was thus about 8 times the rate in the corresponding general population.

Family informants are more likely to remember the existence of maternities of twins versus singleton maternities. However, all our data were according to official information from the church archives. Therefore our data on maternal age and birth order are conclusive. Miscarriages of gestations with twins in an early stage but not noted in the records have not been included in our series. The increased twinning rate seems not to be due to increased maternal age of the female JHND patients. The 4 JHND-mothers got their 5 twin sets relatively young (mean age 30.6 years), because the majority of the affected females were taken seriously ill or died before the most twinning-prone age around 38 years.

Both dizygotic [5] and monozygotic twinning in humans [11, 31] appears to run in families. The increased rate of multiple maternities after ovulation induction in anovulatory women [17] suggests that the immediate physiological cause of the tendency to multiple ovulations is alternation in the mother's hormone levels, and this is supported by recent data, showing that the primary cause of multiple ovulation in humans is not a decrease but an increase in inhibin secretion from the ovary. The increased secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) in mothers of twins may be caused by elevated secretion of, or sensitivity to gonadotropin-releasing hormone (GnRH). The elevated inhibin and midfollicular estradiol (E_2) levels are a response to increased gonadotropin release [26].

In our families with JHND no traits associated with twinning were noted (see below). The increased incidence of multiple maternities, particularly of dizygotic twinning, suggests hereditary tendencies [5, 10, 31]. However, in addition to hormonal induction, environmental factors as maternal age, parity, certain isolate and rural culture, increase the twinning rate [5, 10-13, 21-23, 26]. High twinning rates have been found in Finland among mothers of triplets (38/1000, i.e. about 2.6 times the rate in general population) and in sibships of mothers of triplets (22/1000). In the Åland archipelago (1740-1939) the incidence of twinning in sibships of triplets was among the highest reported in family studies (80/1000) but with wide confidence intervals (95% CI = 19.8 – 88.6; 99% CI = 13.9 – 100.2) and in this insular the twinning rate was also in the general population one of the highest known among whites 19.2/1000 [10, 13].

So far we know, any hereditary disease has not been found convincingly to increase the incidence of multiple maternities. Therefore it is paradoxical that in a fatal disorder, like JHND, the twinning rate is exceptionally high. It may be caused in one or an other way by the pathogenetic process of JHND, e.g. by disturbed lipid metabolism or changed neurohormonal regulation, both possibilities are yet unrevealed. Before neuropsychiatric symptoms begin at about age 30, JHND patients are mentally sound. Factors that may destroy the foundations of marriage of the patients are features of frontal lobe syndrome (e.g. lack of judgement, inconsiderate use of money, neglect of duties, lack of social inhibition, sexual irresponsibility), which often is combined with impotence or frigidity [18-19]. In our JHND patients such behaviour disturbances were observed in only one

patient during the phase of reproduction. However, that does not exclude the possibility that premorbid cerebral (hypothalmic?) lesions were responsible for hormonal changes including polyovulation and twinning.

There may be linkage between the loci in the JHND gene and those genes which supposedly predispose to twinning and other multiple maternities. The locations of these genes are still unknown. In the literature there are very few family trees reported with JHND. In the pedigree reported by Bird et al. [4] there were no twins among the 7 children of a male patient and the 2 children of a female patient. More prospective and epidemiologic studies are needed to further elucidate the incidence of twinning in families with JHND.

Traits associated with twinning

Superfetation twinning. The rare phenomenon of superfetation with dizygotic twinning may occur as a result of continuing ovulation and implantation after the initiation of an other pregnancy [28, 33]. The autosomal dominant gene is transmitted by males as well as females, suggesting that it is primarily expressed at the level of placenta rather than at the level of the mother's hypothalamus and ovary. The twin pairs of our families affected by JHND showed no marked discordance in birth weight and gestational age, which is typical of superfetation.

Malformations. Compared to singletons twins have almost a 50% greater likelihood of congenital malformation [24], but there are rather few malformations for which there is evidence of an association with twinning: congenital heart disease, acardia, and probably single umbilical artery [3], and oesophageal atresia [8]. Oesophageal atresia has not been reported in the recently noted iatrogenically induced association between the use of methylene blue in amniocentesis of twin pregnancies and atresia or stenosis of the ileum and jejunum at birth [9].

Neural tube defects (NTD). There are reports of an excess of twins amongst the parents of infants with spina bifida. Several findings suggest that some women may be predisposed to deliver both twins and infants with NTD. Pathogenetic factors which are relevant to the origin of MZ twinning, may also be relevant to the origin of at least some instances of anencephaly and other NTD's. As some of the available data on the epidemiology of DZ twinning and NTD suggest just the opposite, further work is needed on this issue [25].

Twinning in teratomas and in fetus in fetu. Although the relationship of teratomas to twinning is a controversial subject, there is general agreement that fetuses in fetu are monozygotic twins of their hosts [38]. However, there is a great need for a better knowledge of associated malformations and twinning in the patients and in their families.

Polymastia. Pierre Marie [32] observed supernumary breasts in 4 generations and noted an association with twinning. This finding has not been confirmed in other families with supernumary or accessory nipples (familial intra-areolar polythelia with mammary hypoplasia). In our families with JHND no supernumary breasts have been noted.

Tapetoretinal degeneration. In families with autosomal recessive tapetoretinal degenerations high frequencies of twins have been reported. Ammann, Klein and Franceschetti [2] noted 3 twin pairs of 24 maternities in a family with typical cases of retinitis pigmentosa and congenital tapetoretinal amaurosis (Leber). Forsius and Eriksson [14] observed that twin maternities occurred in 6 of 15 families showing tapetoretinal abiotrophies. However, considering the scantiness of the series, this was attributed to chance and to the fact that the frequency of twinning has been high on the Åland Islands.

Alpha-1-antitrypsin deficiency. It is puzzling that the frequencies of the protease inhibitor (PI) alleles S and Z are relatively high in Caucasian populations and it has been suggested that these deficiency alleles are associated with increased fertility. In mothers of DZ twins the frequency of the S allele was double that in controls (4.4. per cent) [6]. We have not tested the PI types of NHD-patients, but the S allele has a relatively low incidence in Finland [15].

Fragile-X syndrome. Fryns [16] reported that carriers with the Martin-Bell syndrome or fra (X) in Belgium had a high fertility and a fourfold increase in DZ twinning and interpreted that this may be an indication of constitutional or acquired disturbed corticohypothalmic-hypophyseal axis. Also Sherman et al. [35] noted an increased twinning rate among obligate carriers of the fragile X syndrome in Australia (New South Wales), though this may be explained by increased maternal age in the sample of maternities investigated. A high rate of twinning has not been found in fragile-X carriers in the Netherlands [37] and in Finland (J. Leisti, 1990). In our families with JHND no cases with fragile-X were observed.

Lyonisation, genetic imprinting, and mitotic crossing over. The growing number of case reports of female monozygotic (MZ) twins, discordant for an X-linked disorder (Duchenne muscular dystrophy, etc.), suggest that the twinning process and lyonisation (X-chromosome inactivation) are interrelated in a temporal or mechanistic manner that mitotic crossing-over may be associated with twinning and that the mechanism involving an early postzygotic mitotic crossing-over is much more likely than is random lyonisation alone to explain the observed MZ twin discordance of X-linked disorders [7].

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