Scripta Scientifica Medica, vol. 30 (1998), pp. 43-47

GENERIC COUNSELING IN PATIENTS WITH NEUROLOGICAL DISEASES

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Hereditary neurological diseases nowadays are the object of intensive clinical-genetic and molecular-genetic research. In retrospective evaluation of 500 families we find out that 20 of them (4 %) are with genetically determined neuropathology. Spinal muscular atrophy and progressive muscular dystrophy (Duchenne and Becker) predominate but there are families with neural muscular atrophy, Friedreich's ataxia, neurofibromatosis, Strumpel spastic paraparesis, myopaties (inborn and Tompson's) and Huntington's chorea. Mainly the neurological and the paediatric Clinics refer patients. Only one of the visits to the Counseling center is a result of the social contacts of the patients. Almost all autosomal dominant traits segregate in the corresponding pedigrees. Only in three families it is possible to result from a new mutation. The well-known diseases with autosomal recessive and X-linked recessive inheritance are most often sporadic cases. In two pedigrees genetic counseling is a base for prenatal ultrasound diagnosis and in one – for DNA analysis. In the rest cases genetic prognosis is made for some family members. The concrete cases and the problems of the genetic counseling are discussed.

Key-words: Genetic counseling, neurological diseases, autosomal recessive inheritance, X-linked recessive inheritance, diagnosis, prognosis

Hereditary neurological diseases nowadays are object of intensive clinico-genetic and molecular-genetic research. This is imposed from one hand to clarify the link between the differences in the clinical manifestation of one and the same entity and the polymorphism of the hereditary factors which determine it, while on the other hand the revealing of the molecular basis for the expression of certain diseases of the nervous system mark the ways for their correction and prevention.

The present study looks at the problems of the genetic counseling and its results in families with diseases of the nervous system.

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MATERIAL AND METHODS

Data from the Medico-genetic Counseling Centre of the Medical University of Varna are used. The study is retrospective and covers the last 500 families who have been referred to the Centre. Among these hereditary neuropathology has been found in 20 families (4 %). The probands and their affected relatives are 52 altogether. Having in mind the average incidence of the hereditary neurological diseases (1), this is 1/5 of the expected number of affected individuals for the region (about 250). None of them is an offspring of a consanguous marriage. According to the clinical entity and the type of inheritance, the probands are distributed as follows (Table 1):

Table 1

Probands' distribution according to the type of inheritance of the disease

Disease	Type of inheritance*	Number of families
1. Progressive muscular dystrophy (PMD)		
Duchenne	XR	5
Becker	XR	1
2. Spinal muscular atrophy (SMA)		
I and II type	AR	5
3. Friedreich's ataxia	AR	1
4. Myopathy		
inborn	AD	1
Tompson's	AR	1
5. Strumpel spastic paraparesis	AD	1
6. Huntington's chorea	AD	1
7. Neurofibromatosis	AD	1
8. Neural muscular atrophy (NMA)	AD	1
9. Neural muscular atrophy (Charcot-Marie-Tooth)	sporadic	2

* Data originated from other authors (2,3).

The genetic counseling of patients with neurological diseases had the task to:

1) compare the clinical diagnosis with the established for the corresponding clinical entity type of inheritance; 2) determine the genetic risk for the close relatives of the proband; 3) give the family information about the genetic load of the pedigree and the

eventual possibilities for prenatal diagnosis in each case, and 4) give the proband and his close relatives the right to make their own decision concerning their future reproduction (as a result of the received and explained clinical and genetic information).

In three consulted families with PMD each of the probands has one pheno- and genotypically healthy brother. Practically, this estimates a very low genetic risk for the brothers (of 0 %) to transmit the disease to the next generations. The two sisters of the patients with Duchenne MD carry 50 % risk for heterozygosity, while the risk for the daughter of the patient with Becker MD is 100 %. (Fig. 1). DNA analysis in these families is recommended so that prevention of PMD in the offspring of the proven carriers of the pathological gene could be done.

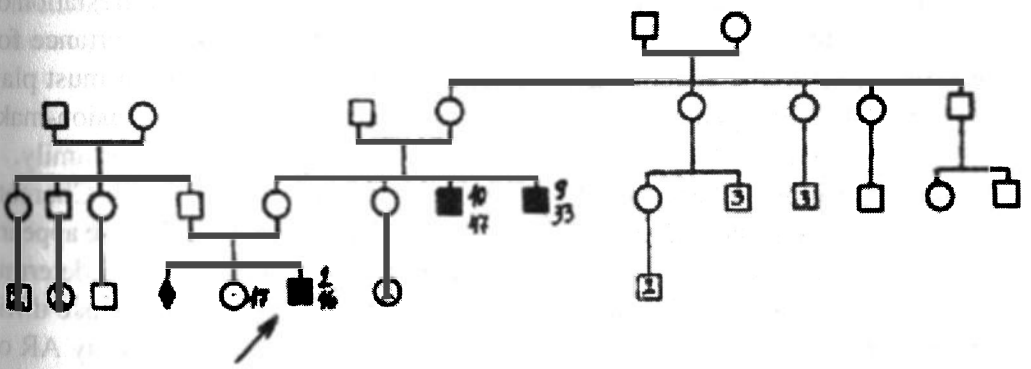

Fig. 1. Genetic tree in Duchenne MD

The AR type of inheritance of SMA determines a high genetic risk (of 25 %) for the siblings of each of the counseled probands. In three of the families SMA, type I or II is the diagnosis in two children in each family. Two families have proceeded DNA testing while the third one has refused (Fig. 2). The molecular investigation gives real possibility for prevention of SMA during the next pregnancies in these families. The other two families have had a single child with SMA. The parents visited the genetic counseling after the death of the affected child that made the DNA testing of the families impossible. The only possible approach for prevention then remained the ultrasound following-up the pregnancy in order to ascertain malformations during embryogenesis and regular following-up the child after birth by neurologist.

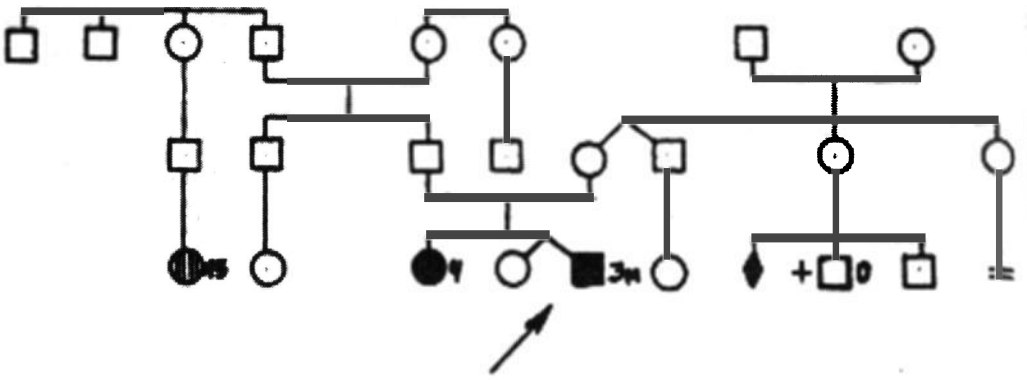

Fig. 2. Genetic tree of SMA

In the families with other AR hereditary neurological diseases (Friedreich's ataxia and Tompson's myopathy one each) the genetic counseling found out a low genetic risk for phenotypic expression of the pathological gene in the close relatives of the probands. Obviously, the AD-diseases perform a very high genetic risk. Thus Strumpel spastic paraparesis and the AD variant of NMA was found out in three consequent generations of the counselled pedigrees, and neurofibromatosis and AD-inborn myopathy – in four. It is important to emphasize that besides the extent of the genetic risk the severity of the clinical manifestation of the disease is of great importance for the genetic prognosis and it must play an appropriate role in the decision-making of the consultant and the family.

In two families with Charcot-Marie-Tooth NMA the disease appears sporadically which makes the determination of the type of inheritance difficult (it might be AD and rarely AR or XR). Thus evaluating the genetic risk and the drawing-out the genetic prognosis for the relatives of these probands is impossible (Fig. 3).

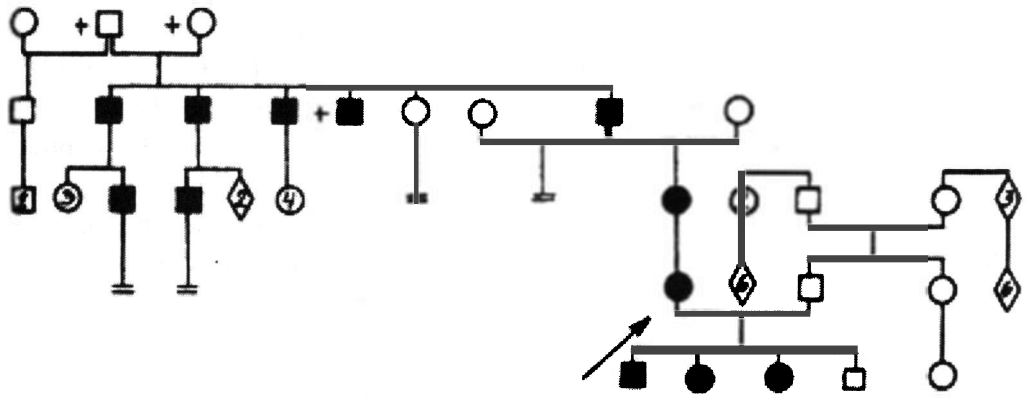

Fig. 3. Genetic tree of NMA - Charkot-Marie-Tooth

In conclusion, we would like to underline that 75 % of the patients with hereditary neuropathology who visited the Medico-Genetic Counseling Centre of the Medical University of Varna were referred for consultation by neurologists, 20 % - by pediatricians, and 5 % did it by their will. In our opinion, the collaboration between clinicians and geneticists should expand in order to lead (when this is possible) to successful prevention of these diseases.

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Медико-генетично консултиране при пациенти с нервни заболявания

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Резюме: Днес наследствено детерминираните нервни заболявания са обект на интензивни клинико-генетични и молекулно-генетични проучвания. При ретроспекция на 500 фамилии ние установяваме, че 20 от тях (4 %) са с генетично обусловена невропатология. Преобладават спиналните мускулни атрофии и прогресивните мускулни дистрофии (Дюшен и Бекер), но са наблюдавани и семейства с неврални мускулни атрофии, спиноцеребеларна атаксия на Фридрайх, неврофиброматоза, спастична парапареза на Щрюмпел, миопатии (вродена и на Томпсън) и хорея на Хънтингон. Болните са насочвани най-вече от Катедрата по неврология, а също и Катедрата по педиатрия. Само едно от посещенията в МГКЦ е провокирано от социалните контакти на консултиращия се. Почти всички автозомно-доминантни форми са с генеалогични данни за сегрегиране в съответните родословия. Само в 3 семейства е възможно да се касае за нововъзникнала мутация. Известните като автозомно-рецесивни и Х-свързани рецесивни заболявания най-често са спорадични случаи. При 2 обследвани рода генетичната консултация е база за пренатална ултразвукува диагностика, а при 1 - за ДНК-анализ. В останалите се прогнозира за някои членове на фамилиите. Дискутира се по конкретните казуси и проблемите на генетичното консултиране.