LETTER TO JMG

Predictive testing in the context of pregnancy: experience in Huntington's disease and autosomal dominant cerebellar ataxia

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Presymptomatic (PT) and prenatal testing (PNT) for Huntington's disease (HD) have been available since 1986. Testing was initially based on genetic markers linked to the disease locus on chromosome 4p.¹ Since 1993 and the identification of the *huntingtin* gene, direct analysis provides accurate PT and PNT.² Recent advances in the field of molecular genetics has provided suitable tools for direct testing in an increasing number of hereditary neurodegenerative disorders, such as autosomal dominant cerebellar ataxias (SCA for spinocerebellar ataxias).^{3–7}

Huntington's disease and SCA are both associated with severe neurological handicap and a progressive course of the

disease. The onset is usually in adulthood and many people at risk have already completed their families when requesting PT. However, for others, future family planning is a frequent motive for requesting PT, either because subjects at risk do not want to give birth to a child with a 50% risk of being affected, or because they would rather not have children if they were a carrier.^{8–13} Several authors have studied the incidence of pregnancy and PNT after PT and showed that the frequency of PNT was quite low among adult onset diseases.^{14–18} In contrast, pregnancies in couples at risk who were requesting PT has not been studied. For the parents, the situation is stressful because of the lack of sufficient preparation for an unfavourable result

Table 1 Data of people at risk requesting presymptomatic testing in an ongoing pregnancy compared to those without pregnancy

	Huntington's disease			Autosomal dominant cerebellar ataxia (SCA)		
	Couples at risk with pregnancy (n=38)	Others (n=777)	p	Couples at risk with pregnancy (n=7)	Others (n=46)	p
Sex of the person at risk						
Male	17 (45%)	292 (38%)	NS	4 (57%)	14 (30%)	NS
Female	21 (55%)	485 (63%)		3 (43%)	32 (70%)	
Mean age, y (SD)	30 (6)	33.9 (11)	<0.05	29.9 (5)	33.4 (10)	NS
Range	19–45	7–72		27–39	14–63	
Already having children						
Yes	16 (42%)	378 (52%)	NS	3 (43%)	21 (48%)	NS
No	22 (58%)	349 (48%)		4 (57%)	23 (52%)	
Unknown					2	
Percentage of risk						
50	33 (87%)	723 (93%)	NS	7 (100%)	44 (96%)	NS
25	5 (13%)	52 (7%)		0	2 (4%)	
75*	0	2 (0.3%)		0	0	
Desire to have children as motivation for presymptomatic testing						
Yes	22 (85%)	217 (35%)	<0.01	5 (71%)	18 (40%)	NS
No	4 (15%)	403 (65%)		2 (29%)	27 (60%)	
Unknown	12	157			1	
Presymptomatic procedure completed						
Yes	19 (50%)	440 (57%)	NS	4 (57%)	30 (65%)	NS
No	19 (50%)	337 (43%)		3 (43%)	16 (35%)	

*Both parents of these subjects were affected by the disease.

Table 2 Decision making of the couples according to whether the request was related to the pregnancy or not

Decision	Presymptomatic testing was requested because of the pregnancy		
	No	Yes	p
Had presymptomatic testing*	10	12	NS
Had not had presymptomatic testing	14	8	

*Missing data for one couple.

Figure 1 Age distribution of the candidates at risk for Huntington's disease and autosomal dominant cerebellar ataxias with an ongoing pregnancy.

and the time constraints in PNT. We report our experience, focusing on the important issue of PT in the context of pregnancy.

PATIENTS AND METHODS

Ten centres of the French Group for Presymptomatic Testing in Neurogenetic Diseases received 868 at risk candidates from 1993 for HD and between 1993 to 1997 for SCA. The people at risk were seen in Paris (n=523), Lyon (n=89), Toulouse (n=67), Bordeaux (n=37), Rennes (n=36), Angers (n=35), Marseille (n=31), Montpellier (n=27), Nancy (n=13), and Grenoble (n=10). Candidates were offered pre- and post-test counselling in accordance with the international guidelines, with several multidisciplinary consultations, including a geneticist, a psychologist, a social worker, a genetic nurse, and a neurologist.¹⁹ Statistical comparison of frequencies used the χ^2 test and of means the ANOVA comparison.

RESULTS

Forty-five (5%) of 868 requests for PT referred to our 10 centres occurred in the context of pregnancy (table 1). There were 38 couples at risk for HD and seven for SCA including SCA1 (n=2), SCA2 (n=2), SCA3 (n=2), and SCA6 (n=1). There were significantly more pregnant couples in the SCA group compared to the HD group (7/58 v 38/815, $p<0.05$). Twenty-four at risk persons asked for PT independently of the

current pregnancy, whereas in 20 the request was related to the pregnancy (table 2).

There were 21 men and 24 women at risk. The mean age of the subject at risk in the couples was 30 (SD 6) years at first contact, ranging from 19 to 45 years, significantly younger than the subjects presenting without pregnancy (mean 34 (SD 11) years, range 7- 72, $p<0.05$) (fig 1). Nevertheless, half of the couples already had one or more children, similar to the group without pregnancy (table 1). Two-thirds of the subjects at risk (23/38, data missing for seven) were accompanied by their spouse, significantly differing from the group without pregnancy (277/582, $p<0.01$).

Only three subjects at risk for HD opted for an early termination of pregnancy (<10 weeks of pregnancy) (fig 2). Nine couples (20%) who wanted to know the status of both the at risk partner and the fetus decided to have PT during the pregnancy in order to ask for PNT in case of a bad result. Four carriers for HD requested PNT and all obtained a favourable result. Surprisingly, 33 of the 45 couples opted not to have PT or PNT at that time and to continue the pregnancy. In fact, only 55% (n=18) of them came back after delivery and 36% (n=12) obtained a result. The proportion of those who went through with the test was no higher in the pregnant group (during pregnancy or after delivery) than in the group without pregnancy (23/45 versus 414/751, $p=0.53$). The sex of the patient did not play a role in the decision to have PT or not, since 12 out of 22 who completed PT were women, similar to those who did not (12 women out of 23).

Although two thirds of the pregnancies (26/43, data missing for two) were in the first trimester, the age of gestation did not appear to have a major influence on the decision concerning PT (table 3). Even among the 26 couples in early pregnancy (less than 3 months of gestation), the number of those who completed PT and had a result was small (n=15), with no statistical difference compared to those with a more advanced pregnancy.

DISCUSSION

Five percent of the 868 at risk couples consulting for PT were pregnant, making this situation not rare. Most couples (73%) chose to continue the pregnancy, reporting their decision to undergo PT or not after delivery. The equal proportion of both sexes among the parents at risk was clearly different from the

Figure 2 Decisions of subjects at risk for Huntington's disease and autosomal dominant cerebellar ataxias concerning ongoing pregnancy and presymptomatic testing.

Table 3 Decision making for presymptomatic testing of the couples regarding gestational age of ongoing pregnancy

Decision	Gestation (months)		
	<3	>3	p
Had presymptomatic testing*	15	6	NS
Had not had presymptomatic testing†	11	10	

*Missing data for two women.

†Missing data for one woman.

female predominance observed among the candidates for PT without pregnancy (63%). Not surprisingly, these persons had a younger mean age compared to those going through PT without being pregnant. The right not to be tested had to be balanced with the necessity to be tested as a parent at risk and the request to test the fetus. This needs sufficient time and puts the parents under additional stress. However, it is of interest that for 55% of the candidates (24/44, data missing for one), requesting PT was independent of the pregnancy. This was not considered to be an important factor. Moreover, the at risk situation did not appear to be a major determining factor in the decision concerning the pregnancy. Nevertheless, the relation between the moment when the person at risk was aware of his personal risk and the request for PT may have played a role in the decision making process.

This was the case for four couples who learned about their risk as the pregnancy was already ongoing. One of them asked for an early termination without requesting PT. Two others opted for PT followed by PNT in case of a bad result. One PNT was done and the fetus was not a carrier. Four other couples were in a different situation. They became pregnant while they were already involved in PT. Only one of them went through with the test, while three couples continued the pregnancy without completing PT.

PT, in the context of pregnancy, is a challenging situation limiting the time for reflection, which has been shown to be important in helping the candidates to take a mature and autonomous decision. In our study, most patients chose to continue the pregnancy and a PNT for the current pregnancy was done in only 9% (4/45) of the cases. These data also indicate that even situations that would be perceived to encourage testing, such as an ongoing pregnancy, are not increasing the uptake frequency, which has been shown to be lower than expected.¹⁶⁻²⁰

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