

In search of anticipation in unipolar affective disorder

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Abstract

Controversial evidence exists regarding the presence of the phenomenon of anticipation in affective disorder. To further evaluate this hypothesis on the unipolar pattern of the disease, we examined 21 two-generation pairs of first and second degree relatives with unipolar recurrent major depression. Biases from index-patient and from unaffected sibs were taken into consideration. A significant difference in the age at onset and episode frequency (as measure of disease severity) between parental and offspring generation was observed. The median age at onset of the parental generation was 37 ± 8.2 years compared to 22 ± 8.3 years in the offspring generation ($p=0.001$). The offspring generation also experienced an episode frequency two times greater than the parent generation ($p=0.001$). Anticipation was demonstrated in 95% of pairs regarding age at onset and in 84% of pairs in episode frequency. However, the observation of a birth cohort effect may possibly explain the differences in age at onset between generations in our sample.

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1. Introduction

The phenomenon of anticipation implies a progressively earlier age at onset and increased severity of a familial disease in successive generations of affected family members. This phenomenon has been demonstrated in myotonic dystrophy, fragile X syndrome, fragile X-linked mental retardation, Friedreich's ataxia, Huntington disease, spinobulbar muscle atrophy, spinocerebellar ataxia type 1, spastic paraplegia, dentatorubral-pallidoluysian atrophy and Machado-Joseph disease (Penrose, 1948; Ridley et al., 1988; Harper et al., 1992; Li and el-Mallakh, 1997; Margolis et al., 1999). In these diseases, anticipation has been correlated to dynamic mutations such as expanded

trinucleotide repeat sequences (Miwa, 1994; Paulson and Fischbeck, 1996; Li and el-Mallakh, 1997). This model of mutations may best fit with complex findings originating from twin, adoption and family epidemiologic data on schizophrenia and affective disorders and it may be one of the reasons behind the non-Mendelian polygenic-multi-factorial inheritance pattern observed in these diseases (Petronis and Kennedy, 1995; Souery et al., 1996). On the clinical level, recognition of the phenomenon is important, since it helps better understanding the history of the disease, particularly in multi-affected families, which are most in need for interventions. Genetic counselling, especially, should consider not only morbidity risk, but also the possibility of genetic anticipation in the inheritance of mental illness (Papadimitriou and Dikeos, 1999).

Evidence for anticipation has been reported for the major psychiatric disorders. In bipolar affective disorder (BPAD), it was demonstrated that the disease had a 9–14 years earlier

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age at onset and was 2–3 times more severe in the offspring generation compared with the parent generation (McInnis et al., 1993; Nylander et al., 1994; Grigoriou-Serbanescu et al., 1997; Mendlewicz et al., 1997; Ohara et al., 1998; Visscher et al., 2001). However, no evidence for anticipation in a group of Canadian bipolar families was reported (Merette et al., 2000). Regarding unipolar affective disorder (UPAD), anticipation has also been observed (Engstrom et al., 1995; Ohara et al., 1998; Visscher et al., 2001). In the Engstrom et al. (1995) study, the parent–offspring differences in age at onset and disease severity were evaluated in 31 pairs with unilineal inheritance of UPAD. The offspring generation experienced onset 15.6 years earlier and illness 1.5 times more severe than did the parent generation. Evidence of anticipation regarding age at onset was found in 75–80% of the family pairs. However, while an increase in episodes frequency was observed in 75% of the pairs, evidence in favor of anticipation regarding the severity of the disease was not statistically significant (Engstrom et al., 1995). Anticipation in affective disorders was observed not only in Caucasian populations (McInnis et al., 1993; Nylander et al., 1994; Engstrom et al., 1995; Grigoriou-Serbanescu et al., 1997; Mendlewicz et al., 1997; Visscher et al., 2001), but also in Japanese families (Ohara et al., 1998). In the latter study on 14 UP/UP and 12 BP/UP pairs, a significantly lower age of onset was found between offspring and parental generation, but with regard to disease severity no evidence for anticipation was demonstrated (Ohara et al., 1998). In the most recent study by Visscher et al. (2001) of individuals classified as affected from recurrent major depressive disorder ($n=68$), a fitted ‘generation’ effect was highly significant, which could be interpreted as evidence for an anticipation effect.

In schizophrenia, also, the phenomenon of anticipation has been observed (Basset and Honer, 1994; Asherson et al., 1994), although other studies led to less conclusive results (Stöber et al., 1995).

The findings of all these reports are difficult to interpret in terms of true anticipation because of the main ascertainment biases that may be involved in such studies and which have been identified since very long (Penrose, 1948). A selection of cases with onset in parents and offspring at a simultaneous time may occur because of the short time over which most studies are carried out. Cases where the offspring has a late age at onset and where the parents are available for study are likely to be rare. Moreover, unaffected sibs at the time of a study might develop the disease with late age at onset. Index bias implies selection of early-onset and more severely affected children because they are more noticeable and more likely to come to the attention of the researcher. A cohort effect on age at onset (Klerman et al., 1985; Gershon et al., 1987; Wickramaratne et al., 1989) can explain the differences observed between parent and offspring generations. Also, memory or recall bias of parents, who forget or deny their age at onset (Klerman et al., 1985; Ridley et al., 1988), censoring bias

when the younger generations are assessed over a shorter period of risk than older generations (Vieland and Huang, 1998), as well as quality and quantity of clinical information (availability of higher quality of information from younger generations compared with older subjects) concerning the subject’s illness (Merette et al., 2000) must be taken into consideration.

Regarding molecular investigation, an association between expansion of trinucleotide CAG repeats and BPAD in Swedish and Belgian patients has been reported (Lindblad et al., 1995) using the Repeat Expansion Detection method (RED-method) (Schalling et al., 1993). The results of this study, which were since then replicated in different samples (O’Donovan et al., 1995, 1996; Oruc et al., 1997; Mendlewicz et al., 1997; Vincent et al., 2000), showed for the first time in a major psychiatric disorder a length of CAG repeats significantly higher in patients compared to normal subjects. However, no correlation between maximum product size of CAG/CTG repeats and age at onset was observed in BPAD (O’Donovan et al., 1996). In a family study, Mendlewicz et al. (1997) have found that the mean trinucleotide CAG repeat length between parental and offspring generation was significantly increased, when the severity of the disease increased, i.e. changed from major depression, single episode or unipolar recurrent depression to bipolar affective disorder. A parent-of-origin effect was also observed with a significant increase in median length of CAG repeats between the parental generation (G1) and the offspring generation (G2) with maternal inheritance (Mendlewicz et al., 1997). On the other hand, no association between length of CAG repeats measured by RED method and severity of illness or age at onset of BP disorder has been found (Craddock et al., 1997), while other studies have failed to demonstrate an increase in repeat expansions (Zander et al., 1989; Visscher et al., 2001). In one study employing UPAD patients, the RED method failed to detect any CAG expansion compared to controls, but the number of patients was relatively low (the analysis was successful in 39 patients) and only nine of all patients had positive family history for affective disorder (Oruc et al., 1997).

The aim of the present study was to evaluate the hypothesis of anticipation in UPAD with special attention to limit selection biases.

2. Subjects and methods

Data were collected from 20 families of two or three generations containing at least two subjects with UPAD. These pedigrees were originally identified for linkage studies. Each subject was examined by a psychiatrist to establish or exclude any psychiatric disorder. Diagnosis was confirmed by use of the Schedule for Affective Disorders and Schizophrenia-Lifetime Version (SADS-L), which provides diagnoses based on the Research Diagnostic

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