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Search and commentary

Article reviewed: Restless legs syndrome in monozygotic twins: clinical correlates ☆

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Objectives

Determine for monozygotic twins the concordance of expression and the similarity of clinical features of RLS.

Study design

Clinical case study and retrospective review of clinical records.

Study population

Twelve monozygotic twins. Nine twins were identified by one twin responding to an announcement in a national publication of an RLS patient organization, three were identified from the authors' large clinical population. A secondary population was also used consisting of all patients in the authors' clinical database of RLS patients (1996–2000) with only one potential gene donor of known gender.

Methods

The primary analyses were based on identification of subjects self-reporting having both a diagnosis of RLS and a monozygotic twin. Genotyping for 11 highly polymorphic markers (14–20 alleles, heterozygosity of 0.65–0.86) was used to support the monozygotic relationship. The clinical and family history was obtained for each twin by both interview and subsequent questionnaire. RLS severity was assessed using a 40-point rating scale. The RLS diagnosis was based on the International Restless Legs Study Group diagnostic criteria. Serum ferritin levels were obtained at the same time of day for each twin.

Secondary analyses relied mostly on records from a large clinical database reviewed for familial RLS with only one parent with RLS ($n = 50$).

Results

All twin pairs showed identical genetoyping for all 11 markers. RLS concordance occurred for ten of the 12 pairs (83%). Other family members with RLS were identified in 11 of the 12 pairs. Only one twin appearing to be sporadic with no other relative affected. No agreement was found for the ten concordant twins for age-of-symptom onset or RLS severity. There was no apparent relation to gender of parent with RLS. Serum ferritin did not relate to RLS severity.

The secondary analyses of family history of RLS patients with one parent with RLS showed no relation between age-of-symptom onset and gender of the parent (average of 26 for father and 29 for mother

☆ William G. Ondo, Kevin Dat Vuong, Quing Wang, (Neurology, 2000;55:1404–1406)

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with RLS). The age-of-symptom onset was reported to be much older (47 years) for 42 RLS patients without a family history of RLS. No other information is provided on these 42 patients and no statistical analyses were made using their data.

Conclusions

The data indicate a high degree of concordance not related to gender of the parent with variable degree of age of onset and severity. The results are consistent with a highly penetrant, autosomal dominant inheritance with apparently other genetic or environmental factors affecting age-of-onset and severity. No relation to gender of the parent with RLS was found for either the twins or the larger retrospective family history series of 50 Thus these data suggest gender is not a significant factor in the family history of RLS.

Comment

These data are particularly valuable since they are the first on the concordance of RLS among identical twins and since this is a highly respected clinical group very experienced in the diagnosis and treatment of RLS. Their finding of a very high rate of concordance is consistent with the commonly held view that RLS has a highly penetrant, autosomal dominant inheritance. These are probably the best data yet supporting this genetic view of RLS. These data also make it unlikely there is a sex-linked transmission.

It is, however, important to remember that this type of study is more informative if it is negative. A high concordance rate can occur for either strong genetic, environmental or genetic-environmental interactions. In fact, the reported heterogeneity for age-of-symptom onset and RLS severity could be seen as supporting a more complex genetic and environmental basis for RLS. The author's conclusions somewhat overstate their case, since other control data such as a comparison with concordance for heterozygotic twins is needed to determine degree of heritablity. This is particularly the case for common disorders such as RLS which occurs in 5–15% of some populations and also for studies such as this one where the twins are self-identified with the disorder rather than selected from a large population base. These twins may reflect a particular subset of the disorder or may have a strong response bias favoring concordance.

The authors may have also somewhat overstated their conclusions from their negative results given the small sample size. The failure to find similar age-of-symptom onset or RLS severity within a twin pair must be accepted cautiously. The very limited sample size of only ten pairs gives for a directional hypothesis a probability of Type II error >0.20 except for very strong correlation >0.80. Since these types of clinical data inherently have considerable reporting error, even a very strong biological relationship may have only a modest degree of correlation. Nonetheless, the disparate values found for a couple of the twins make it seem unlikely a larger sample size will lead to a different conclusion. The failure to find a significant relationship between serum ferritin and RLS severity in this report is a somewhat more substantive finding since it can be based on 20 cases. But even for a sample of 20 the type II error exceeds 0.20 for correlation ≤ 0.5, which is about the level of correlation reported in other studies. Conclusions from negative results are usually a problem especially from small samples and although these negative results are based on very low correlation, the authors probably should have more clearly recognized the sample size problem. They did provide perhaps the best remedy for small sample size data and presented in a table all of the basic clinical data on the 12 twin pairs. This greatly enhances the value of this article.

Thus overall, this study provides important data marking the way for future studies. The strong twin concordance indicates that there is some strong factor operating in RLS. While it seems highly likely that the genetic factor plays a major role in such a strong effect, further studies are needed to determine the degree of the genetic component. There is a now a long list of RLS studies making the same case. The large pedigrees, the common occurrence in some families, and even the reported relationship between age-of-symptom onset and occurrence in families are strongly consistent with autosomal dominant inheritance at least for some RLS, but unfortunately these published studies fail to meet modern standards for adequate population genetics. In the face of all of these tantalizing studies and the persisting failure to identify a gene it is time for a well-controlled population genetic study

of RLS. In fact, it is somewhat surprising that despite the strong claims made over the past 10 years none of the basic genetic population studies have been done that would support the certitude of the claims. There is, for example, still no systematic blinded, controlled study of the family history in a population of RLS patients, nor has there been any controlled twin or adoption studies nor any segregation analysis performed. This is particularly a problem given the large number of reported sporadic cases of RLS (40% or more) [1–3], which hardly seems compatible with the data in this study suggesting high penetrance. The current authors note, however, that carefully excluding secondary RLS decreased the rate of sporadic RLS to 8% in one of their clinical populations, a value more consistent with this high concordance rate [2]. This uncertainty in the literature about the number of sporadic cases again underscores the need for a well-controlled family history study of RLS conducted by one of the clinical groups very experienced with RLS diagnosis.

While well-controlled population genetic studies are hard to do, the high twin concordance data in this important study indicates the need for now doing these basic studies to confirm the hypothesized genetic pattern. Until they are done or until we have some gene or genes identified for RLS we must remain somewhat cautious in making claims regarding patterns of inheritance and the magnitude of the genetic contribution.

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