Original article

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Increased clinical anticipation with maternal transmission in benign adult familial myoclonus epilepsy in Japan

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ABSTRACT – We recently reported clinical anticipation in Japanese families with benign adult familial myoclonus epilepsy (BAFME). However, it remains unknown whether clinical anticipation is predominantly associated with paternal or maternal transmission. We investigated the relationship between gender of the transmitting parent and clinical anticipation in nine BAFME families. Clinical anticipation regarding either cortical tremor or generalised seizures was observed in all 12 parent/child pairs (8 mother/child pairs and 4 father/child pairs). Moreover, a higher degree of clinical anticipation was associated with maternal transmission than with paternal transmission (p=0.03). Although a causative gene for BAFME still remains unknown, our finding suggests that BAFME and diseases with unstable expanding repeats, including those in non-coding regions, might share a similar molecular mechanism because such diseases often show clinical anticipation with maternal transmission.

Key words: benign adult familial myoclonus epilepsy (BAFME), clinical anticipation, maternal transmission

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Benign adult familial myoclonus epilepsy (BAFME) is an autosomal dominant disease characterised by cortical tremor and infrequent generalised seizures. According to electrophysiological studies, BAFME manifests as cortical reflex myoclonus (Ikeda *et al*., 1990; Yasuda, 1991; Terada *et al*., 1997). BAFME has been reported in the last two decades to manifest with various terms, such as cortical tremor (Ikeda *et al*., 1990), BAFME (Yasuda, 1991), and familial adult myoclonic epilepsy (Plaster *et al*., 1999) in Japan, and familial cortical myoclonic

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tremor with epilepsy (van Rootselaar *et al*., 2005) and autosomal dominant cortical tremor, myoclonus, and epilepsy (Striano *et al*., 2005) in Europe.

Regarding the genetics of BAFME, Japanese families were shown to demonstrate linkage to chromosome 8q (Plaster *et al*., 1999), whereas European families demonstrated linkage to chromosomes 2p (Striano *et al*., 2004) and 5p (Depienne *et al*., 2010). In addition, a founder effect was reported in European families (Madia *et al*., 2008), but not in Japanese families. However, a causative gene for BAFME still remains unknown.

There tends to be an increase in severity and decrease in onset age with vertical transmission, a phenomenon known as anticipation We recently reported early-onset age of either cortical tremor or generalised seizures, or appearance of generalised seizures in the next generation in four BAFME families (Hitomi *et al*., 2012). Our finding suggested that the triplet repeat is a possible genetic abnormality associated with BAFME, since an inverse proportional relationship between the number of triplet repeats (genetic anticipation) and onset age of symptoms (clinical anticipation) has previously been reported for dentatorubral-pallidoluysian atrophy (DRPLA) (Ikeuchi *et al*., 1995), other autosomal dominant cerebellar ataxias (Manto, 2005), and myotonic dystrophy (Ashizawa *et al*., 1992), amongst others. In triplet repeat diseases, the gender of the transmitting parent has a significant effect on anticipation. Anticipation was predominantly associated with paternal transmission in some polyglutamine diseases, such as DRPLA (Ikeuchi *et al*., 1995), but was predominantly associated with maternal transmission in myotonic dystrophy (Ashizawa *et al*., 1992). If BAFME shares a similar molecular mechanism with that of triplet repeat diseases, clinical anticipation in BAFME might also be affected by the gender of the transmitting parent. Although our previous analysis showed no clear relationship between clinical anticipation and gender (Hitomi *et al*., 2012), this might have been due to the small number of parent and child pairs studied. To further this initial study, by adding additional five families, we investigated the relationship between the gender of the transmitting parent and clinical anticipation in Japanese patients with BAFME, which might suggest a possible molecular mechanism for BAFME.

Materials and methods

Previously, we reported 4 BAFME families with clinical anticipation (Hitomi *et al*., 2012). In this study, a total of 9 Japanese BAFME families were investigated corresponding to the 4 families previously reported together with an additional 5 families. We retrospectively identified 12 parent/child pairs (8 mother/child pairs and 4 father/child pairs) based on onset age or appearance of cortical tremor and generalised seizures across generations (*table 1*). Diagnostic criteria for BAFME were adopted from our previous study (Hitomi *et al*., 2011).

Clinical anticipation was defined as an earlier onset age, by more than 10 years, of either cortical tremor or generalised seizures, or appearance of these symptoms in the next generation. In order to further clarify the degree of clinical anticipation, we graded the clinical anticipation as follows: earlier onset of clinical symptom in the next generation by 10-19 years (1+), 20-29 years (2+), and 30-39 years (3+). Families 1-4 in *table 1* were reported in our previous study (Ikeda *et al*., 2005; Hitomi *et al*., 2011; Hitomi *et al*., 2012). Many of the parent/child pairs were directly interviewed or examined by the authors, but some of them were indirectly interviewed. These studies were performed as part of the patients' clinical evaluation in Kyoto University Hospital.

In order to evaluate effects associated with gender of the transmitting parent, we compared the occurrence ratio of clinical anticipation between father/child pairs and mother/child pairs using the chi-square test. The level of statistical significance was set at $p<0.05$.

Results

In total, 22 patients (10 men and 12 women, ranging from 21 to 76 years) were investigated. Among them, 21 patients showed cortical tremor and 15 patients showed infrequent generalised seizures. The onset age of cortical tremor was from 15 to 59 years and that of generalised seizures was from 19 to 62 years. Giant somatosensory evoked potentials (SEPs) were observed in 11 of 12 patients. Anticonvulsants, mainly clonazepam and valproic acid, were administered for the treatment of both cortical tremor and seizures. These characteristics were relatively consistent with our previous reports (Hitomi *et al*., 2011; Hitomi *et al*., 2012).

Results are summarised in *table 1* and *figure 1*. Among 12 parent/child pairs showing clinical anticipation, 8 were mother/child pairs and 4 were father/child pairs. Clinical anticipation for cortical tremor occurred in 5 of 8 mother/child pairs and 3 of 4 father/child pairs (*table 1* and *figure 1A*). With regards to generalised seizures, clinical anticipation occurred in 5 of 8 mother/child pairs and 3 of 4 father/child pairs. Clinical anticipation as new onset of generalised seizures in the next generation occurred in 4 of 8 mother/child pairs and 1 of 4 father/child pairs (*table 1* and *figure 1B*). Clinical anticipation for both cortical tremor and generalised seizures was observed in 4 of 12 parent/child pairs (2 of 8 mother/child pairs and 2 of 4 father/child pairs). There

Table 1. Summary of parent/child pairs.

Parent/child pair		Clinical anticipation	
		Cortical tremor	Generalised seizure
Family 1	mother/child	3+	3
Family 2	mother/child	-	+*
Family 3	mother/child	2+	-
Family 4	mother/child	-	+*
Family 4	mother/child	-	+*
Family 6	mother/child	1+	-
Family 8	mother/child	1+	+*
Family 9	mother/child	2+	-
Family 2	father/child	1+	1+
Family 3	father/child	2+	+*
Family 5	father/child	1+	-
Family 7	father/child	-	1+

*: appearance of generalised seizure in the next generation.
1+: earlier onset of clinical symptoms in the next generation by 10-19 years; 2+: earlier onset of clinical symptoms in the next generation by 20-29 years; 3+: earlier onset of clinical symptoms in the next generation by 30-39 years.

was no significant difference simply in the occurrence rate of these parameters between mother/child pairs and father/child pairs.
However, a higher degree of clinical anticipation, *i.e.* i) onset of generalised seizures or ii) earlier onset age, by more than two decades (2+, 3+), of either cortical tremor or generalised seizures, was more frequently observed in 7 of 8 mother/child pairs than in 1 of 4 father/child pairs (p=0.03) (*table 1*).

Discussion

In this study, we have further demonstrated that clinical anticipation exists in the Japanese BAFME families. In addition, a higher degree of clinical anticipation was more frequently associated with maternal transmission than with paternal transmission. This suggests that BAFME and diseases in which anticipation predominantly associates with maternal transmission might share a similar molecular basis. As mentioned in the introduction, polyglutamine diseases, in which anticipation is associated with paternal transmission, show expansion of triplet repeats in coding regions. On the other hand, myotonic dystrophy and other diseases, in which anticipation is associated with maternal transmission, also show expansion of triplet repeats in non-coding regions. Taken together, BAFME and diseases with unstable expanding repeats, including those in non-coding regions, might share a similar molecular mechanism. One reason why the causative gene for BAFME has not easily been discovered in the last two decades, despite extensive gene analysis, could be the fact that it lies within non-coding regions. Clinical anticipation was also observed, to some extent, in the father/child pairs, which is at least partially consistent with the fact that paternal transmission was also observed in patients with myotonic dystrophy of triplet repeat disease, despite an unknown mechanism (Zeesman *et al.*, 2002).
On the other hand, we could not find clear evidence that clinical anticipation is associated with more severe disease progression, since no clear inverse relationship between onset age and symptom severity of cortical tremor was found either in our pervious study (Hitomi *et al.*, 2012) or this study. Thus, clinical anticipation would largely appear to effectively lower symptom threshold. However, this conclusion is limited by the fact that severity of cortical tremor was evaluated at different ages for each individual patient, because they were diagnosed at different ages, thus the interval between onset and diagnosis of cortical tremor was

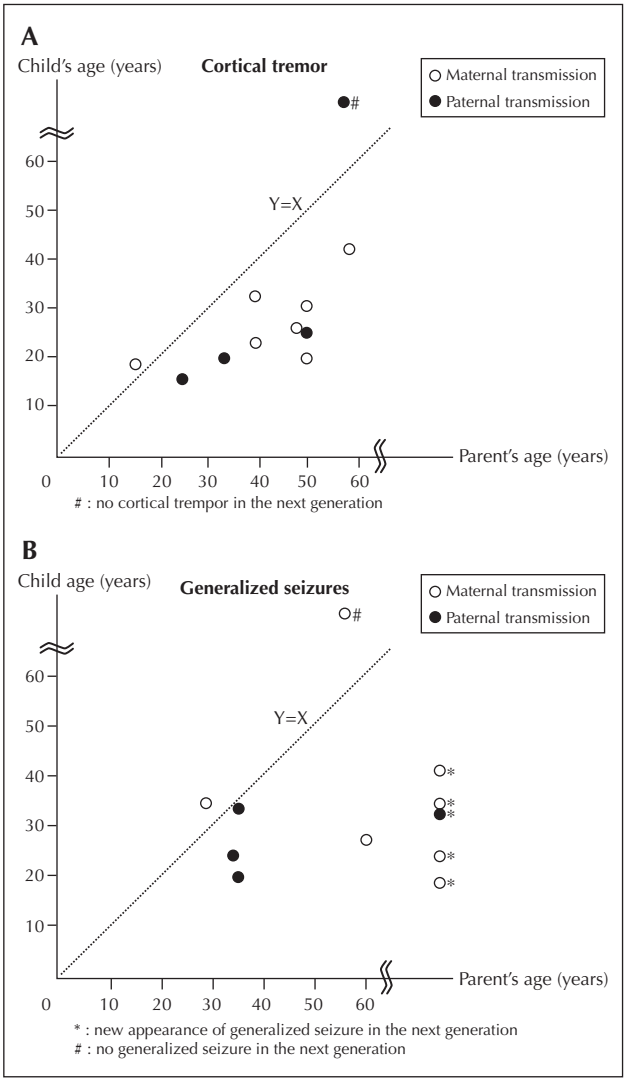

Figure 1. Onset age of both cortical tremor (A) and generalised seizures (B) for each parent (X axis) and child (Y axis) pair.
For cortical tremor, anticipation was associated with both paternal and maternal transmission, and earlier onset age of cortical tremor by more than two decades occurred frequently in mother/child pairs (A). Two of 8 mother/child pairs showed exactly the same onset age, thus the data demonstrating maternal transmission is presented based on 7 mother/child pairs with different onset age. Regarding generalised seizures, anticipation was associated with both paternal and maternal transmission, and earlier onset age, by more than two decades, or onset of generalised seizures frequently occurred in mother/child pairs (B). (For one mother demonstrating maternal transmission, cortical tremor started within the second decade of life, therefore the onset age of the mother was plotted as 15 for convenience [A]).

not considered. A prospective study is warranted to further clarify this point.
There were some limitations in this study. First, the number of parent/child pairs investigated was relatively small. Therefore, we could not show a statistically significant difference in the occurrence rate of clinical anticipation for cortical tremor or generalised seizures. Second, our findings were based on only clinical information and were not supported by laboratory data. However, our findings were relatively consistent, at least within the studied parent/child pairs, thus an earlier diagnosis due to earlier recognition of symptoms could not fully explain our findings. In addition, inappropriate treatment is also a possible cause of earlier identification of the symptoms, since life-threatening myoclonic status could occur after the administration of gabapentin in a patient with European BAFME (Striano *et al*., 2007). However, this is not relevant to our study, because our patients were not treated with gabapentin, but treated mainly with clonazepam and valproic acid. Third, not all patients underwent gene testing for DRPLA, however, the diagnosis of DRPLA in the studied parent/child pairs is highly unlikely because of the lack of cerebellar ataxia or progressive cognitive impairment, as well as the presence of so-called "giant SEPs". Future gene analysis may enable us to further understand this apparent clinical feature more comprehensively. □

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References

Ashizawa T, Dubel JR, Dunne PW, *et al*. Anticipation in myotonic dystrophy. II. Complex relationships between clinical findings and structure of the GCT repeat. *Neurology* 1992; 42: 1877-83.

Depienne C, Magnin E, Bouteiller D, *et al*. Familial cortical myoclonic tremor with epilepsy: the third locus (FCMTE3) maps to 5p. *Neurology* 2010; 74: 2000-3.

Hitomi T, Ikeda A, Kondo T, *et al*. Increased cortical hyperexcitability and exaggerated myoclonus with aging in benign adult familial myoclonus epilepsy. *Mov Disord* 2011; 26: 1509-14.

Hitomi T, Kondo T, Kobayashi K, Matsumoto R, Takahashi R, Ikeda A. Clinical anticipation in Japanese families of benign adult familial myoclonus epilepsy. *Epilepsia* 2012; 53: e33-6.

Ikeda A, Kakigi R, Funai N, Neshige R, Kuroda Y, Shibasaki H. Cortical tremor: a variant of cortical reflex myoclonus. *Neurology* 1990; 40: 1561-5.

Ikeda A, Kurihara S, Shibasaki H. Possible anticipation in BAFME: three generations examined in a Japanese family. *Mov Disord* 2005; 20: 1076-7.

Ikeuchi T, Koide R, Tanaka H, *et al*. Dentatorubral-pallidoluysian atrophy: clinical features are closely related to unstable expansions of trinucleotide (CAG) repeat. *Ann Neurol* 1995; 37: 769-75.

Madia F, Striano P, Di Bonaventura C, *et al*. Benign adult familial myoclonic epilepsy (BAFME): evidence of an extended founder haplotype on chromosome 2p11.1-q12.2 in five Italian families. *Neurogenetics* 2008; 9: 139-42.

Manto MU. The wide spectrum of spinocerebellar ataxias (SCAs). *Cerebellum* 2005; 4: 2-6.

Plaster NM, Uyama E, Uchino M, *et al*. Genetic localization of the familial adult myoclonic epilepsy (FAME) gene to chromosome 8q24. *Neurology* 1999; 53: 1180-3.

Striano P, Chifari R, Striano S, *et al*. A new benign adult familial myoclonic epilepsy (BAFME) pedigree suggesting linkage to chromosome 2p11.1-q12.2. *Epilepsia* 2004; 45: 190-2.

Striano P, Zara F, Striano S. Autosomal dominant cortical tremor, myoclonus and epilepsy: many syndromes, one phenotype. *Acta Neurol Scand* 2005; 111: 211-7.

Striano P, Coppola A, Madia F, *et al*. Life-threatening status epilepticus following gabapentin administration in a patient with benign adult familial myoclonic epilepsy. *Epilepsia* 2007; 48: 1995-8.

Terada K, Ikeda A, Mima T, *et al*. Familial cortical myoclonic tremor as a unique form of cortical reflex myoclonus. *Mov Disord* 1997; 12: 370-7.

van Rootselaar AF, van Schaik IN, van den Maagdenberg AM, *et al*. Familial cortical myoclonic tremor with epilepsy: a single syndromic classification for a group of pedigrees bearing common features. *Mov Disord* 2005; 20: 665-73.

Yasuda T. Benign adult familial myoclonic epilepsy (BAFME). *Kawasaki Med J* 1991; 17: 1-13.

Zeesman S, Carson N, Whelan DT. Paternal transmission of the congenital form of myotonic dystrophy type 1: a new case and review of the literature. *Am J Med Genet* 2002; 107: 222-6.