Genetic anticipation in Behçet's syndrome

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Abstract

Objective—To examine the presence of genetic anticipation in families with Behçet's syndrome (BS).

Methods—A total of 18 families with 40 affected members in two successive generations were evaluated by interviewing them for their ages at the onset of the first symptom of BS and for their ages at the time they fulfilled the diagnostic criteria.

Results—It was noted that the age of onset of the first symptom was lower in the second generation in 14 families ($p=0.01$) with a mean (SD) age of 20.57 (7.47) years in the children compared with 33.29 (9.92) years in the parents ($t=7.79$, $p<0.0001$), whereas the diagnostic criteria were fulfilled at an earlier age in the children in 15 families ($p=0.01$) with a mean age of 21.2 (6.74) years in the children compared with 36.4 (9.55) years in the parents ($t=7.41$, $p<0.0001$).

Conclusion—Genetic anticipation was present in 15 of 18 (84%) of the families with BS in the form of earlier disease onset in the children compared with their parents.

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Behçet's syndrome (BS), originally described as recurrent oral and genital ulcerations and uveitis, is a vasculitis of unknown aetiology.¹ The syndrome is associated with HLA Bw51 in certain populations.² Familial cases have been noted but the exact nature of the transmission and the precise genetical bases of the illness have not been determined.³

Genetic anticipation is an epidemiological phenomenon with a molecular basis characterised by earlier disease onset or increase in disease severity, or both, in successive generations. It is observed in various disorders such as myotonic dystrophy, bipolar affective disorder, schizophrenia, rheumatoid arthritis, and Crohn's disease.^{4–8} At least in certain diseases of monogenic origin such as myotonic dystrophy, anticipation seems to be related to an expansion of unstable trinucleotide repeats.⁹

We looked for genetic anticipation among our large population of BS patients, all attending a dedicated BS outpatient clinic operating for the past 20 years.

Patients and methods

The charts of 2853 patients attending our outpatient clinic at the Rheumatology Department of Cerrahpaşa Medical School were reviewed. Twenty one families who had at least one member affected in two successive generations were identified. One family was later excluded

from the study because the parent did not fulfil the diagnostic criteria¹⁰ although she had oral aphthae and a few inflammatory cells in her vitreous. Two of these families could not be contacted because they had moved and their addresses were unknown. The affected members ($n=40$) of the remaining 18 families were seen at their homes ($n=20$), in the hospital ($n=14$) or were contacted by telephone ($n=4$). They were interviewed by one of us (IF). The information on two of the patients was obtained from their children because one was deceased and the other did not want to contact the physician. Their ages at the time of onset of their first symptom, the nature of their symptoms, and the time they first applied for medical care were recorded. A clinical activity index was calculated for each patient, using the criteria shown in table 1.¹¹

There was one affected child and his/her parent in each generation in 16 families, two affected children and one parent in one and three affected children and one parent in one family.

Five of the parents had previously been diagnosed elsewhere and did not have a chart in our registry while the remaining patients were initially evaluated and periodically seen in our outpatient clinic.

To control for a possible cohort effect, the charts of 11 to 12 consecutive patients not belonging to these families were selected for each year starting from 1978 from our registry of 2853 patients with BS. They were evaluated for their ages at which their initial symptoms appeared and at the time they fulfilled their diagnostic criteria. For this purpose the charts of 67 patients seen between 1977–1983, 56

Table 1 Total clinical activity index (the index for the individual patient is the numerical sum of clinical features)

Eye	
0	normal
1	cells in vitreous and/or anterior chamber only
2	vision 50%
3	vision 30%
4	able to see few feet
5	blind
Skin	
1	aphthae
1	erythema nodosum
1	genital ulceration
Vascular involvement	
1	unilateral calf vein thrombosis (cvt) and/or superficial thrombophlebitis (tb)
2	bilateral cvt and/or tb
3	cvt and/or tb requiring bed rest
4	thrombosis of vena cava superior (vcs) or vena cava inferior (vci)
5	thrombosis of vcs and vci and/or arterial occlusion
Arthritis	
1	for each joint
Neurological involvement	
2	intracranial hypertension
4	multiple sclerosis like syndrome
5	pyramidal and/or cerebellar involvement

Table 2 Clinical features of the families who showed genetic anticipation (n=33)

Parent			Child			Parent			Child			Parent		
Sex	Symptom (AO)	CAI	Sex	Symptom (AO)	CAI	Sex	Symptom (AO)	CAI	Sex	Symptom (AO)	CAI	Sex	Symptom (AO)	CAI
1 M	OA (38) EYE (38) MS (38)	7	M	OA (29) EN (29) MS (29) OF (29) GU (29)	4	6 M	OA (31) GU (33) OF (33) EN (33) EYE (33)	7	M	OA (11) MS (11) EN (11) EYE (13)	6	11 F	OA (20) GU (20) OF (30) EN (30) EYE (45)	4
2 M	OA (16) MS (16) OF (20) GU (27) EYE (27) EN (30)	8	F	OA (12) GU (12) EN (12) EYE (12)	6	7 F	OA (22) GU (22) EN (22) MS (22) EYE (34)	5	M	OA (17) OF (17) EN (15)	2	12 F	OA (46) OF (47) GU (47) MS (47) EYE (47)	5
3 F	OA (30) GU (29)	2	F	OA (13) GU (19) MS (20) EN (20) EYE (21)	5	8 M	OA (38) GU (38) EN (39) OF (39) MS (39)	6	M	OA (21) OF (21) EN (21) MS (21) GU (23) EYE (25)	10	13 M	OA (38) GU (38) OF (38) EYE (38) PA (44)	8
4 M	OA (30) GU (30) EYE (38) MS (41)	5	M	OA (19) GU (19) OF (19) MS (20)	4	9M	OA (49) GU (49) EN (49) EYE (52)	8	M	OF (39) MS (39) EYE (39) GU (40) OA (41)	5	14 F	OA (30) GU (30) MS (40) EN (48)	4
5 M	OA (32) GU (32) EYE (32) MS (33)	8	M	NEU (22) GU (23) EN (25) OA (25) TB (25)	11	10 F	OA (18) GU (34) OF (34) MS (34)	3	F	OA (17) GU (18) OF (18) MS (18)	3	15 F	OA (46) GU (46) EN (56)	3

M= male, F= female, CAI= clinical activity index, AO=age of onset, OA= oral apthae, EN= erythema nodosum, MS= musculoskeletal involvement, OF= ostiofolliculitis, U= genital ulcer, EYE= uveitis, TB= thrombophlebitis, NEU= neurological involvement.

between 1984–1988, and 66 between 1989–1994 were analysed.

The files of all of the patients belonging to our BS registry, were also retrospectively evaluated for the frequency of horizontal familial cases.

In the familial patients, the qualitative differences of the ages of onset and ages at the time of diagnosis between generations were evaluated by the sign test, whereas the quantitative differences and the clinical activity indices were compared with the paired *t* test. The differences of the ages of the non-familial patients were analysed by the ANOVA test.

Results

When all the families who showed vertical transmission (n=18) were evaluated regardless of the presence of genetic anticipation, the mean (SD) age at onset of the first symptom was 20.72 (6.84) years in the children compared with 30.61 (10.18) years among the parents (*t*=5.15, *p*<0.0001) whereas the mean age at the time of diagnosis was 22.89 (7.08) years in the children compared with 34.22 (10.27) years in the parents (*t*=4.52, *p*<0.0001).

The age of onset of the first symptom of the syndrome was lower in the second generation in 14 families (*p*=0.01) with a mean (SD) age of 20.57 (7.47) years in the children compared with 33.29 (9.92) years in the parents (*t*=7.79, *p*<0.0001). The diagnostic criteria were fulfilled at an earlier age in the children in 15 families (*p*=0.01) with a mean age of 21.2 (6.74) years in the children compared with 36.4 (9.55) years in the parents (*t*=7.41, *p*<0.0001). There were no significant differences in the ages of onset and at diagnosis between the parents and children in the remaining three families.

Table 2 shows the clinical characteristics, ages at the onset of symptoms, and the clinical activity indices of the members of the 15 families who show the pattern of genetic anticipation (n=33).

The most frequent early symptoms in the parents and children consisted of mucocutaneous findings; a manifestation that is present in up to 97% of the cases with BS.¹²

The first generation had presented earlier at our clinic for medical attention in 14 of 15 families who showed the pattern of genetic anticipation.

Among the families who had an earlier onset in the children, male to male transmission was present in seven, female to female in three, male to female in one, and female to male in four patients. There was no correlation between parental or paternal age at conception and the age of onset of the symptoms of their children (respective *r* and *p* values 0.28, 0.3 and 0.09, 0.8). The disease activity scores of the parents and children did not differ significantly (*t*=0.72, *p*=0.48).

When the charts of 189 patients attending our outpatient clinic, who did not belong to the families mentioned above, were evaluated for age at first symptom and age at diagnosis, it was seen that the mean age at the first symptom between 1978–1983, 1984–1988, and 1989–1994 were respectively 25.31 (7.08), 25.4 (9.5), and 26.14 (8.6) years (*F*=0.82, *p*=NS) and the mean ages at diagnosis were 28.02 (7.09), 27.95 (9.23), and 29.9 (9.4) years (*F*=0.34, *p*=NS). The mean ages at which the first symptom appeared and that at the time of diagnosis for the whole group (n=189) were 25.65 (8.3) and 28.69 (8.6) years.

The frequency of the horizontal and vertical familial cases in our registry was found to be 3.6% (117 of 2853) on retrospective evaluation.

Table 2 continued

Child			Child			Child		
Sex	Symptom (AO)	CAI	Sex	Symptom (AO)	CAI	Sex	Symptom (AO)	CAI
M	OA (16) OF (20) EN (20) GU (24) MS (25) OA (25) GU (25)	4	F	OA (14) GU (14)	2	F	OA (15) GU (15)	2
M		2						
M	OA (22) OF (22) EYE (22)	3						
M	OA (19) GU (19) OF (19) MS (28)	3						
F	OA (24) GU (24) EYE (25) EN (25)	7	F	OA (19) GU (21) OF (21) EN (21) EYE (21)	7			

Discussion

Our data suggest that genetic anticipation was present in 15 of 18 families (84%) with BS. Several sources of bias that can mimic anticipation need to be considered before drawing a definite conclusion.

The first generation had presented for medical attention before the second generation in 14 of the 15 families, the members of which showed a pattern of genetic anticipation. This earlier awareness of disease could have led to the increased alertness of the parents resulting in an earlier diagnosis in their children. It should be noted that the children and parents in five of these families, including the one in which the second generation had presented earlier, were living in separate homes at the time of diagnosis.

Another potential source of bias is that the parents may have forgotten the exact date their symptoms emerged. Ten of these parents had initially presented to our outpatient clinic and five of them were diagnosed elsewhere and were not routinely being followed up in our department. When the original notes in the charts of the patients who had been followed up in our department were compared with the data obtained during the interviews, no major contradictions concerning the dates their symptoms emerged were evident.

The earlier disease onset in the second generation as observed in our study might also be related to an external factor that emerges earlier in the life span of the second generation when compared with the first (the cohort bias). However there is no reason to suspect this as supported by the rather uniform onset of the syndrome with respect to age among the patients used as controls.

The earlier death of patients with severe disease is another epidemiological factor that may have influenced our results by causing the pre-

ferential ascertainment of patients with later onset of disease. However this seems unlikely in BS because the rate of mortality of this disease is somewhat low.¹³

There seemed to be no difference in the severity of the disease among the two generations and factors related to sex did not seem to play a part in transmission. The parental and paternal age at conception was not related in any way to the age of onset of the first symptom in the children. The changes may be subtle however and given the limitations of a retrospective study conducted in a reference centre, more hospital and community based cases have to be examined before coming to a conclusion concerning this issue. It should also be kept in mind that an increase in severity of the disease in the second generation or a negative correlation between the paternal age at conception and the age at first symptom are not indispensable features of the definition of genetic anticipation. We must also acknowledge that there are still no properly validated and internationally accepted activity and severity indices for BS, although substantial effort has been put to this.¹⁴

The average age at the time of diagnosis was higher in the parents and lower in the children of our families with BS, compared with the ages observed in our non-familial cases with BS (36.4 (9.55) years and 21.2 (6.74) years compared with 28.69 (8.69) years). There was no reason to account for this difference and a similar phenomenon was not described in other diseases with genetic anticipation. However, a control group consisting of non-familial cases was not used in these studies.⁴⁻⁸

The frequency of all the familial cases in our registry of BS was 3.6% when examined retrospectively and reached 8% in a prospective study.¹⁵ Thus, it is clear that our finding of genetic anticipation is relevant only for a small fraction of these patients.

Clues for genetic anticipation in BS as noted in this study, suggest that expansion of unstable trinucleotide repeats may form the genetic basis of the defect in familial cases. Until now at least nine disorders showing genetic anticipation were found to be associated with these dynamic mutations.¹⁶ Further research is thus warranted to understand the underlying genetic defect in familial BS, especially with regard to trinucleotide repeats.

- 1 Yazici H. Behçet's Syndrome. Klippel JH, Dieppe PA. *Textbook of Rheumatology*. London: 1994: Mosby, 6. 20. 1-6.
- 2 Ohno S, Ohguchi M, Hirose S, Matsuda H, Wakisaka A, Aizawa H. Close association of HLA Bw51 in Behçet's disease. *Arch Ophthalmol* 1982;100:145-58.
- 3 Bird Stewart JA. Genetic analysis of families of patients with Behçet's syndrome; data incompatible with autosomal recessive inheritance. *Ann Rheum Dis* 1986;45:265-8.
- 4 Harper PS, Harley HG, Reardon W, Shaw DJ. Anticipation in myotonic dystrophy: new light on an old problem. *Am J Hum Genet* 1992;51:10-16.
- 5 McInnis MG, McMahon FJ, Chase GA, Simpson SG, Ross CA, DePaulo JR Jr. Anticipation in bipolar affective disorder. *Am J Hum Genet* 1993;53:385-90.
- 6 Bassett AS, Honer WG. Evidence for anticipation in schizophrenia. *Am J Hum Genet* 1994;54:864-70.
- 7 Mc Dermott E, Khan MA, ARC UK National Repository, Deighton C. Further evidence for genetic anticipation in familial rheumatoid arthritis. *Ann Rheum Dis* 1996;55:475-7.
- 8 Polito JM II, Rees RC, Childs B, Mendeloff AI, Harris ML, Bayless TM. Preliminary evidence for genetic anticipation in Crohn's disease. *Lancet* 1996;347:798-800.

- 9 Richards RI, Sutherland GR. Heritable unstable DNA sequences. *Nature Genet* 1992;1:7–9.
- 10 International Study Group for Behçet's disease. Criteria for the diagnosis of Behçet's disease. *Lancet* 1990;335:1078–80.
- 11 Yazici H, Tüzün Y, Pazarlı H, Yurdakul S, Özyazgan Y, Özdoğan H, et al. Influence of age of onset and patient's sex on the prevalence and severity of manifestations of Behçet's syndrome. *Ann Rheum Dis* 1984;43:783–9.
- 12 Jorizzo JL, Abernethy JL, Wain IW, Mangelsdorf HC, Zouboulis CC, Sarica R. Mucocutaneous criteria for the diagnosis of Behçet's disease: an analysis of clinicopathological data from multiple international centers. *J Am Acad Dermatol* 1995;32:968–76.
- 13 Yazici H, Baaran G, Hamuryudan V, Hizli N, Yurdakul S, Mat C, et al. The ten year mortality in Behçet's syndrome. *Br J Rheumatol* 1996;35:139–41.
- 14 Hamuryudan V, Fresko I, Direskeneli H, Tanrıverdi M, Akoglu T, Yurdakul S, et al. Inter and intraobserver reliability of the Turkish translation of the Behçet's disease activity form. *Rev Rhum Engl Ed* 1996;63:541.
- 15 Tüzün Y, Yazici H, Pazarlı H, Yalçın B, Yurdakul S, Müftüoğlu A. The usefulness of the non-specific skin hyperreactivity (the pathergy test) in Behçet's disease in Turkey. *Acta Dermatovenereologica (Stockholm)* 1979;59:77–9.
- 16 Ashley CT, Warren ST. Trinucleotide repeat expansion and human disease. *Annu Rev Genetics* 1995;29:703–28.