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BRIEF COMMUNICATION

Susceptibility and HLA-B27 in post-dysenteric arthropathies

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Summary. A recent outbreak of bacillary dysentery in The Netherlands revealed that, despite the close association of HLA-B27 with post-dysenteric or reactive arthritis (ReA), not even in one family did all HLA-B27 positive patients infected by an arthritogenic bacterium, develop ReA. This dissociation shows that additional factors beside B27 may determine susceptibility to ReA.

Several forms of post-infectious or reactive arthritis (ReA) are closely associated with HLA-B27 (Keat, 1983). Laboratory studies indicate that certain enterobacterial antigens might be directly involved (Ebringer, 1983). Despite these findings, it remains unexplained why only a minority of infected B27$^+$ patients develop ReA (Calin, 1985). Certain recently identified variants of the B27 antigen (Grumet *et al.*, 1982; Breur-Vriesendorp *et al.*, 1985; Taurog *et al.*, 1985) might convey higher susceptibility to ReA than others (Grumet *et al.*, 1985), perhaps due to similarity with certain B27-like moieties on the infectant (van Bohemen, Grumet & Zanen, 1984). The dissociation of B27 and ReA in three families with dysentery, described below, suggests that additional factors are also involved.

Abbreviation: ReA, post-infectious or reactive arthritis.

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Shigella flexneri 2a was absorbed by ELISA onto immulon 96-well micro-elisa plates (Dynatech, Alexandria, VA) for 24 hr at 37° (0·5 mg/well). Plates were rinsed three times with phosphate-buffered saline (PBS) containing 0·5% Tween-80, after which any remaining non-specific binding sites blocked with 3% essentially globulin-free bovine serum albumin (BSA, Sigma, St Louis, MO). Serial dilutions in PBS–0·1% BSA were incubated in quadruplicate at 37° for 1 hr. After rinsing three times in PBS–Tween, anti-human immunoglobulin peroxidase conjugate (Tago, Burlingame, CA) was incubated for 1 hr at 37°, and after rinsing five times, fresh substrate was added. The reaction was stopped after 15 min and the optical absorbance was measured with a multiscan micro-elisa reader (Flow Laboratories, Irvine, Ayrshire, U.K.). Each plate contained a row of substrate controls and a calibration curve.

A recent outbreak of *S. flexneri* 2a dysentery in The Netherlands affected about 120 citizens. The State Health authority traced the source of the infection back to a batch of contaminated South-East Asian Shrimps. All members of the families shown in Table 1 ate these shrimps, and all but one (K) displayed serum titres to *S. flexneri* in at least one immunoglobulin class. In one family, three children (C, D and F) developed dysentery, one child (E) did not suffer from diarrhoea, and both parents had mild diarrhoea. The children C, D and F were B27-positive (B27$^+$) and developed severe ReA and conjunctivitis; their B27$^+$

Table 1. Antibodies to *Shigella flexneri* 2a in three families with post-dysenteric arthropathies

Patients	Age	Sex	Dysentery	SF*	HLA-B27	ReA†	IgM‡	IgA‡	IgG‡
Controls§ ($n=35$)	23–59	18♀	–	–	ND¶¶	–	29±4	3±1	9±1
Family 1									
Patient A	54	♀	+	ND	–	–	57±9	2±1	26±4
Patient B	60	♂	+	ND	+	–	6±1	43±14	14±2
Patient C	29	♀	++	+	+	+	116±27	138±44	182±29
Patient D	27	♂	++	+	+	+	224±36	9±3	251±40
Patient E	25	♀	–	ND	–	–	9±1	1±1	19±3
Patient F	17	♀	++	+	+	+	724±116	1639±17	268±43
Family 2									
Patient G	57	♂	+	–	+	–	2±1	3±1	19±5
Patient H	42	♀	+	–	+	–	24±1	16±2	19±1
Patients I	19	♀	+	–	+	+	288±49	158±55	339±7
Family 3									
Patient J	60	♂	+	–	+	–	10±2	11±4	63±10
Patient K	55	♀	+	–	–	–	8±2	2±1	7±1
Patient L	27	♀	+	+	+	+	871±137	1432±38	564±75

Antibody titres were estimated in acute phase sera by ELISA.
*S. *flexneri* 2a isolated from the faecal carriage.
† ReA, reactive arthritis.
‡ Percentage of standard serum ± standard error.
§ Controls consisted of hospital patients without known arthropathies or gastrointestinal disease.
¶¶ ND, not determined.

father did not. A similar dissociation of B27 and ReA occurred in two other three-member families involved in this outbreak. Both families consisted of a $B27^+$ daughter developing severe ReA, whereas both $B27^+$ parents in one family and the $B27^-$ mother and $B27^+$ father in the other family developed dysentery, but remained free of joint symptoms. In total, the outbreak involved 13 $B27^+$ patients, of which only the above five, (C, D, F, I and L) developed ReA. Apparently, additional factors beside certain B27 variants, predispose to ReA. These could be (i) age-related susceptibility, (ii) recessive susceptibility genes in close linkage disequilibrium with B27 on chromosome 6 as proposed for ankylosing spondylitis (Dick *et al.*, 1974; Van der Linden *et al.*, 1975), or (iii) dominant non-linked disease resistance genes interacting with B27 or B27-linked susceptibility genes. Also, although less likely, it cannot be excluded that some family members ate more infected shrimps than others and therefore received a heavier infective inoculum.

Interestingly, antibody titres were relatively low in the four $B27^+$ subjects without ReA (B, G, H and J) and high in the five $B27^+$ individuals with ReA (C, D, F, I and L). This suggests that the strength of the antibody response, perhaps ruled by one of the above factors, might determine whether ReA develops. These high titres may include antibodies to B27-like antigenic epitopes (as is currently under investigation) thus giving rise to ReA via the cross-reactivity concept as proposed by Ebringer (1983). Although the identification of *Shigella* cell envelope antigens with epitopes that cross-react with certain B27-like moieties supports direct involvement of certain B27 variants defined by these moieties in the aetiology of ReA (Ebringer, 1983; van Bohemen *et al.*, 1984), it seems that one or more of the above options are also involved. Disease expression in ReA might be a multigene effect, possibly involving both B27 and a closely linked gene. The families described above show that B27 does not appear to be the sole major susceptibility factor in *S. flexneri*-related ReA.

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