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ABO/Secretor genetic complex and susceptibility to asthma in childhood

F. Ronchetti*, M.P. Villa*, R. Ronchetti*, E. Bonci*, L. Latini*, R. Pascone#, N. Bottini¶, F. Gloria-Bottini+

ABO/Secretor genetic complex and susceptibility to asthma in childhood. F. Ronchetti, M.P. Villa, R. Ronchetti, E. Bonci, L. Latini, R. Pascone, N. Bottini, F. Gloria-Bottini. ©ERS Journals Ltd 2001.

ABSTRACT: A positive association has recently been reported in adult subjects between O/nonSecretor phenotype and asthma. To confirm this association, this study investigated the joint ABO/Secretor phenotype in a cohort of 165 asthmatic children. Three-hundred and sixty-two consecutive newborn infants from the same population were also studied as controls.

The proportion of O/nonSecretor in asthmatic children was higher than in controls, thus confirming the association found in adults. The association was more marked in males than in females. In males, the pattern of association between the joint ABO/Secretor phenotype and asthma is dependent on the age at on-set of symptoms.

Since the oligosaccharide composition of cell membrane and mucosal secretions is controlled by the cooperative interaction of ABO and Secretor genes, and since such composition influences the adhesion of infectious agents, the age pattern could reflect a more general interaction between developmental maturation and oligosaccharide structure concerning their effects on susceptibility to viral and bacterial agents.

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*Institute of Pediatric Clinic, #Child Health, University of Rome "La Sapienza", Rome, ¶Depts of Internal Medicine, Division of Allergology and Clinical Immunology and +Biopathology and Imaging Diagnostics, Division of Preventative and Social Paediatrics, University of Rome "Tor Vergata", Rome, Italy.

Correspondence: F. Gloria-Bottini, Dipartimento di Biopatologia e Diagnostica per Immagini, Università di Tor Vergata, Via della Ricerca Scientifica, Roma, Italy, 00133
Fax: 39 672596028

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The Secretor gene (FUT2) that encodes for a 2-alpha-L-fucosyltransferase and the ABO blood grouping system that encodes for glycosiltransferases, act in concert to build-up oligosaccharide structures in exocrine secretion systems, including the respiratory tract [1, 2, 3].

Specific oligosaccharide epitopes are necessary for recognition of micro-organisms [4]. The product of ABO and Secretor genes seems to influence the adhesion of infectious agents, thus having a modulatory effect on viral and bacterial respiratory infection [3, 5].

A combined analysis of ABO blood groups and salivary Secretor phenotypes was recently performed in a cohort of coal miners. Lower lung function and higher prevalence of wheezing and asthma in non-Secretor subjects of blood group O was shown.

The present study analysed the joint phenotype ABO/Secretor in a cohort of asthmatic children in an attempt to confirm the association observed in adult subjects.

Subjects and methods

The sample study is composed of 165 children, 109 males and 56 females, aged 1 month – 15 yrs. The patients were observed in the outpatient paediatric pulmonary clinic of the University of Rome "La Sapienza" or were admitted to a ward of the same clinic for acute respiratory episodes. Both subsamples were consecutive.

The criterion for inclusion in the study was a history of two or more episodes of wheezing in the last 6 months, irrespective of the aetiology/pathogenesis of the attack. A consecutive series of 362 newborn infants from the same population of Rome was considered as a control sample.

ABO and Secretor phenotypes were determined according to standard laboratory procedures [6]. Differences of ABO and Secretor phenotype distribution between asthmatics and controls, and association between ABO and Secretor phenotypes were evaluated by the Chi-squared test of independence. Differences of the joint ABO/Secretor phenotype among age classes at on-set in asthmatic children and controls were evaluated by the Chi-squared test of independence.

Results

Table 1 shows, for males and females, the joint ABO/Secretor phenotype distribution in asthmatic children and in consecutive healthy newborns from the same population. The ABO phenotype frequencies in asthmatic children do not differ significantly from controls. Conversely, the frequency of Secretor

phenotype is significantly lower in asthmatic children than in controls. This difference is significant in males only. In asthmatic children there is also an association between ABO and Secretor phenotype frequencies, again significant only in males.

Table 2 shows the proportion of O/nonSecretor phenotype in asthmatic children and in controls. The proportion is higher in asthmatic than in normal children and the difference is much more marked in males than in females.

Table 3 shows the proportions of the joint ABO/Secretor phenotypes grouped in four categories in relation to age at on-set of asthma. Only male subjects have been considered in this analysis. In relation to age at on-set of clinical manifestations, children were grouped into three categories: 1) on-set in the first year; 2) on-set between 2 and 5 yrs and; 3) on-set after 5 yrs. However, since the last group only includes nine subjects, it has not been considered for all statistical analyses. The distribution of the joint ABO/Secretor phenotypes differs not only between asthmatic and normal children, but also within the asthmatic group.

Table 4 shows the relative risk values of joint ABO/Secretor phenotypes in asthmatic children belonging to on-set age groups 1) and 2). O/nonSecretor children have a high value of relative risk in both groups, while non-O/Secretor children show a relative risk very near to 1, suggesting a neutral behaviour. The other two joint phenotypes show significant differences concerning the relative risk. Thus, non-O/nonSecretors seem to be more susceptible to asthma in the first year of life and protected in the following years, while O/Secretor individuals seem to be protected against asthma in the first year of life and neutral in following years.

Table 1. – Distribution of joint ABO/Secretor phenotype in asthmatic children and in healthy newborns (controls).

Phenotype	Males		Females	
	NonSecretor	Secretor	NonSecretor	Secretor
Asthmatics				
A	7 (20.6)	32 (42.7)	5 (33.3)	15 (36.6)
B	5 (14.7)	8 (10.7)	0 (0.0)	4 (9.8)
AB	0 (0.0)	6 (8.0)	1 (6.7)	1 (2.4)
O	22 (64.7)	29 (38.7)	9 (60.0)	21 (51.2)
Total	34 (31.2)	75 (68.8)	15 (26.8)	41 (73.2)
Controls				
A	10 (23.8)	57 (37.0)	10 (30.3)	52 (39.1)
B	8 (19.0)	19 (12.3)	5 (15.2)	16 (12.0)
AB	2 (4.8)	9 (5.8)	1 (3.0)	2 (1.5)
O	22 (52.4)	69 (44.8)	17 (51.5)	63 (47.4)
Total	42 (21.4)	154 (78.6)	33 (19.9)	133 (80.1)

Data are presented as number of subjects (per cent of subjects). A, B, AB and O refer to blood groups. The only asthmatic versus control significant differences were for numbers of male secretors ($p=0.05$) and total number of secretors ($p<0.05$). Significant associations between ABO and secretor phenotypes were for male asthmatics ($p<0.025$) and total number of asthmatics ($p<0.10$).

Table 2. – Per cent proportion of O/non secretor phenotype in healthy and asthmatic children.

	Asthmatics %	Controls %	p-value
Both sexes	18.8	10.7	0.01
Males	20.2	11.3	<0.05
Females	16.1	10.2	NS

p-values refer to the Chi-squared test, asthmatics *versus* controls.

Discussion

Alpha-2-fucosyltransferases FUT1 (previously termed H) of red cells and vascular endothelium, and FUT2 (previously termed Se) of exocrine secretion system, are structural genes that collaborate with glycosiltransferases. Glycosiltransferases are controlled by the ABO system, to build oligosaccharide structures on the cell surface of erythrocytes and vascular endothelium, as well as in the exocrine secretion system including the respiratory tract [3].

Previous studies based on separate analysis of the ABO and Secretor systems have led to discordant results [3, 7, 8, 9], probably because of the complexity of the epistatic interactions between these genes. A combined analysis of ABO blood groups and Secretor phenotypes has recently shown, in a cohort of coal miners, a cooperative interaction between the two systems. Blood group O/nonSecretor subjects had lower lung function values and higher prevalence of asthma and wheezing [3]. The present data confirm this cooperative interaction concerning susceptibility to asthma in childhood. The association, however, is much more marked in males than in females.

Among the newborn control group, a number of young infants may later develop asthma. In order to evaluate the effects of this bias, a correction factor was introduced under the hypothesis that 10% of new-

Table 3. – Distribution of joint ABO/secretor phenotypes in relation to age at onset of asthma in male children.

Age at onset yrs	ABO/secretor phenotype			
	Nonsecretor/O	Nonsecretor/A, B or AB	Secretor/O	Secretor/A, B or AB
≤ 1 (a)	8 (25.8)	7 (22.6)	3 (9.7)	13 (41.9)
1 – 5 (b)	11 (20.8)	1(1.9)	19 (35.8)	22 (41.5)
>5 (c)	1 (11.1)	2 (22.2)	2 (22.2)	4 (44.4)
Controls (d)	22 (11.2)	20 (10.2)	69 (35.2)	85 (43.4)

Data are presented as number of subjects (per cent of subjects). A, B, AB and O refer to blood groups. Chi-squared test was used to compare groups as follows; a *versus* b *versus* c *versus* d: $p=0.013$; a *versus* b *versus* d: $p=0.003$; a *versus* b: $p=0.005$.

Table 4. – Relative risk of joint ABO/secretor phenotypes in relation to age at onset of asthma.

Age at onset yrs	NonSecretor/O	NonSecretor/A, B or AB	Secretor/O	Secretor/A, B or AB
≤1	2.75 (0.99 – 7.48)	2.57 (0.88 – 7.30)	0.20 (0.06 – 0.71)	0.77 (0.34 – 1.71)
1 – 5	2.07 (0.86 – 4.91)	0.17 (0.02 – 1.24)	1.03 (0.52 – 2.03)	0.93 (0.48 – 1.79)

Data are presented as odds ratios (95% confidence interval). A, B, AB and O refer to blood groups.

borns will become asthmatic during childhood. With such correction, the differences between asthmatic and (true) controls increase, thus improving the level of significance. For example, in table 1, male controls will have a frequency of blood group O nonsecretor equal to 51% (instead of 52.4%) and a frequency of nonSecretor equal to 20.3% (instead of 21.4%).

The analysis of ABO/Secretor types in relation to age at on-set of asthmatic symptoms has revealed an interesting additional pattern of association suggesting that non-O/nonSecretor children are more susceptible in the first year, but not in following years, while the O/Secretor is less susceptible in the first year than in subsequent years. Since at present, it cannot be excluded that the younger age group includes transient wheezers, it is possible that wheezers in the first year include a cluster of subjects well genetically-differentiated from other subjects.

It would be interesting to study the possible relationship of oligosaccharide composition of the cell membrane and of the contiguous secretion layer, with the pattern of common viral and bacterial respiratory infections during the first 5 yrs of life. Susceptibility to classes of micro-organism may depend on interaction between the developmental stage of the individual and oligosaccharide structure of the respiratory mucosa. The association with bronchial asthma could simply be a special aspect of a more general phenomenon.

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