Original article

Male individuals with Robin Sequence: emerging significant association with ABO and RhD blood group phenotypes

Kaique Cesar de Paula Silva, Thiago Silva Messias, Gisele da Silva Dalben, Narciso Almeida Vieira

Universidade de São Paulo (USP), Bauru, SP, Brazil

ABSTRACT

Background: This study investigated the association of Robin Sequence with ABO and RhD blood group phenotypes.

Methods: A retrospective cross-sectional study was performed of a cohort of Robin Sequence patients of the Hospital de Reabilitação de Anomalias Craniofaciais – Universidade de São Paulo (USP), Brazil. The study group was composed of 339 individuals of both genders with Robin Sequence referred for specific treatment. A control group was composed of 1780 individuals without syndromes. The groups were compared using the Pearson’s chi-square test ($\chi^2$) with statistical significance being defined for an alpha error of 5% (p-value < 0.05).

Results: A comparison of gender found a significant difference for the AB phenotype between groups (p-value = 0.007). Comparing blood type by gender there was no significant difference within the same group (p-value = 0.117 and 0.388 respectively, for Robin Sequence and the control group). When comparing the AB blood type between groups, there was no difference for females (p-value = 0.577), but there was a significant difference for males (p-value = 0.0029).

Conclusions: This study showed that the population with Robin Sequence had different patterns related to gender concerning the phenotypic distribution of ABO and RhD blood group phenotypes. Robin Sequence is more common among females. The AB phenotype was significantly higher in males with Robin Sequence than in males of the Control Group. The prevalence of the RhD-negative phenotype is higher in individuals with Robin Sequence. This result suggests a possible association of ABO and RhD phenotypes with Robin Sequence that should be better investigated by molecular studies, as it deserves greater attention.

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Introduction

The ABO and RhD blood group phenotypes are classified by antigens expressed in the erythrocyte glycosylalve and defined by genetic expression. The gene encoding ABO blood group phenotypes is located on the long arm of chromosome 9 and is responsible for a type II protein, a singular amine- or carboxy-terminal plasma transmembrane molecule, which expresses four antigens (A, B, AB and O). The RHD and RHCE genes, located on the short arm of chromosome 1, encode Rh antigens.

The study conducted by Ponce and Valverde demonstrated a relationship between the expression of ABO antigens and the helminth Ascaris lumbricoides, revealing that individuals with the A phenotype are at higher risk of infestation by this parasite. In 2012, a study by Mäkivuoiko et al. demonstrated that individuals with the B phenotype present a greater number of the bacterium Clostridium leptum in the bowel lumen. Storry and Olsson demonstrated a correlation between Plasmodium vivax and the absence of the AB phenotype in individuals of African descent, who present suppression of alleles of the ABO genes causing an absence of the receptor for the malaria parasite in erythrocytes.

The Robin Sequence (RS) is an autosomal recessive craniofacial malformation with intense phenotypic expression, considered a sequential pathogenesis or a non-specific symptomatic complex, which may occur in several situations: in isolation, (isolated RS) or associated with known syndromes including the Stickler, Treacher-Collins and Van der Woude syndromes, or in association with other developmental defects that do not constitute a specific syndrome. The main characteristic of RS is a triad of anomalies: micrognathia (mandibular hypoplasia), glossosotipsis (posterior tongue displacement) and cleft palate causing difficulties in sucking and swallowing that can cause obstruction of the airway and even death in some cases.

The study of Jakobsen et al. of a human cytogenetic database, identified putative chromosomes and genes, 4q32-qter, GAD67 (2q31), PVR11 (11q23-q24), and the SOX9 gene (17q24.3-q25.1), with the latter also being described by Selvi & Mukunda and other authors as playing an important role in RS.

Considering the importance of genetic interactions in blood groups and the lack of studies applied to populations of individuals with RS, this study investigated the association of RS with ABO and RhD blood group phenotypes.

Methods

This study was approved by the Institutional Review Board of the Hospital de Reabilitação de Anomalias Craniofaciais, Universidade de São Paulo (USP) (protocol #665.580). All data of ABO and RhD blood group phenotypes were obtained from secondary sources such as the patients’ medical records. The test is mandatory before any surgical procedure in the institution.

The study group included 339 individuals of both genders with RS registered at the institution. A control group was composed of 1780 individuals without any syndromes, attending appointments in the Ear, Nose and Throat Department. All individuals were Caucasians of Brazilian nationality.

The groups were compared using the Pearson chi-square test with statistical significance being defined for an alpha error of 5% (p-value <0.05).

Results

Among the 339 patients with RS, 45% (153/339) were males and 55% (186/339) were females. Of the 1780 individuals in the control group, 51% (909/1780) were males and 49% (871/1780) were females.

Table 1 shows the comparison between the RS and control groups according to the ABO phenotype. The data revealed a predominance of the O phenotype (47.5% vs. 46.9%), followed by A (34.5% vs. 38.9%), B (11.8% vs. 11%) and AB (6.2% vs. 3.2%), respectively. A comparison of gender found a significant difference for the AB phenotype between groups (p-value = 0.007).

Table 2 shows the comparison between the RS and control groups according to the RhD phenotype. Analysis of the data of both groups showed a predominance of RhD+ (85.3% and 90.2%). Comparison between the RS group and the control group according to the RhD phenotype and genders revealed no significant differences.

Discussion

Craniofacial anomalies, such as cleft lip, cleft palate and RS, are caused by changes occurring during human embryonic development and may be observed in the embryo in the early days of gestation.

The main characteristic of RS is a triad of anomalies comprising micrognathia (mandibular hypoplasia), glossosotipsis (posterior tongue displacement causing pharyngeal obstruction) and cleft palate in nearly 90% of cases of RS.

The clinical presentation of individuals with RS varies widely. Due to these changes, especially in the neonatal period, the child may have problems such as feeding difficulties and breathing disorders, with the possibility of respiratory obstruction or even severe crises of asphyxia, which may lead to death if not promptly managed.

The association of ABO and RhD blood group phenotypes with different diseases is receiving more attention from the scientific community. Studies by Greer et al. demonstrated that individuals with the O phenotype present a significant association with the development of pancreatic cancer.

Harris et al. evidenced that individuals with the O phenotype were more likely to develop symptomatic disease if infected with Vibrio cholerae. Yamagata et al. revealed predominance of the A phenotype in individuals with chronic discoid lupus erythematosus, thereby facilitating the prognosis in disseminated clinical presentations of the disease.

The study of Sharma et al. demonstrated a higher prevalence of malocclusions in individuals with the B phenotype in the population of Jaipur, India. It is important to point out that the present research demonstrated a possible association of RS with ABO and RhD blood group phenotypes. Therefore, it...
Table 1 – Comparison between the Robin Sequence and control group according to the ABO phenotype.

<table>
<thead>
<tr>
<th>Type</th>
<th>Male n (%)</th>
<th>Female n (%)</th>
<th>Total n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>43 (12.7)</td>
<td>74 (21.8)</td>
<td>117 (34.5)</td>
</tr>
<tr>
<td>B</td>
<td>18 (5.3)</td>
<td>22 (6.5)</td>
<td>40 (11.8)</td>
</tr>
<tr>
<td>AB</td>
<td>12 (3.5)</td>
<td>9 (2.7)</td>
<td>21 (6.2)</td>
</tr>
<tr>
<td>O</td>
<td>80 (23.6)</td>
<td>81 (23.9)</td>
<td>161 (47.5)</td>
</tr>
<tr>
<td>Total</td>
<td>153 (45.1)</td>
<td>186 (54.9)</td>
<td>339 (100.0)</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Type</th>
<th>Male n (%)</th>
<th>Female n (%)</th>
<th>Total n (%)</th>
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</thead>
<tbody>
<tr>
<td>A</td>
<td>369 (20.7)</td>
<td>324 (18.2)</td>
<td>693 (38.9)</td>
</tr>
<tr>
<td>B</td>
<td>91 (5.1)</td>
<td>104 (5.8)</td>
<td>195 (11.0)</td>
</tr>
<tr>
<td>AB</td>
<td>29 (1.6)</td>
<td>28 (1.6)</td>
<td>57 (3.2)</td>
</tr>
<tr>
<td>O</td>
<td>420 (23.6)</td>
<td>415 (23.3)</td>
<td>835 (46.9)</td>
</tr>
<tr>
<td>Total</td>
<td>909 (51.1)</td>
<td>871 (48.9)</td>
<td>1780 (100.0)</td>
</tr>
</tbody>
</table>

*p-Value = 0.006.

Table 2 – Comparison between control group and Robin Sequence according to the RhD phenotype.

<table>
<thead>
<tr>
<th>Type</th>
<th>Robin Sequence n (%)</th>
<th>Control Group n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RhD-positive</td>
<td>289 (85.3)</td>
<td>1606 (90.2)</td>
</tr>
<tr>
<td>RhD-negative</td>
<td>50 (14.7)</td>
<td>174 (9.8)</td>
</tr>
<tr>
<td>Total</td>
<td>339 (100.0)</td>
<td>1780 (100.0)</td>
</tr>
</tbody>
</table>

Conclusion

This study was limited to obtaining data from secondary sources, namely from the patients’ medical records. The study concluded that, originally, the population with RS had a different pattern related to gender concerning the phenotypic distribution of ABO and RhD blood group phenotypes. The RS is more common among females. Phenotype AB was significantly more prevalent in male individuals with RS. The prevalence of the RhD-negative phenotype is higher in individuals with RS. Therefore, this result suggests a possible association of ABO and RhD blood group phenotypes with RS. Further studies should be carried out to elucidate possible interactions between genotypes and phenotypes of other erythrocyte antigens besides ABO and RhD in individuals with RS.

Conflicts of interest

This study was supported by the Hospital for Rehabilitation of Craniofacial Anomalies, Universidade de São Paulo (USP), Brazil. Collaboration with statistical data by Ms Flávia Maria Ravagnani Neves Cintra and Hilton Coimbra Borgo PhD.

The authors declare no conflicts of interest.

References


