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Research Article

GENETIC RISK OF RESPIRATORY DISTRESS IN INFANTS

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ABSTRACT

Respiratory distress syndrome (RDS) is one of the main causes of respiratory diseases and mortality among premature newborns. It requires intensive medical care, including mechanical ventilation and surfactant therapy. Timely detection and treatment of RDS are vital to prevent severe complications and improve outcomes in newborns. The study of genetic mutations, such as SFTPB, SFTPC, and ABCA3, which affect the production and function of surfactant, contributes to a deeper understanding of the pathophysiology of RDS and the development of targeted therapies. Treating newborns with RDS requires significant resources, including prolonged stays in neonatal intensive care units, increasing healthcare costs. Understanding genetic predisposition and individual risks for developing RDS allows for personalized approaches to treatment and prevention, improving the quality of medical care. Identifying risk factors such as cesarean section, multiple pregnancies, and maternal diseases helps develop preventive strategies to reduce RDS incidence. Research is ongoing to improve existing treatment methods and develop new therapeutic strategies, such as stem cell and gene therapy, to enhance outcomes in patients with RDS.

KEYWORDS

Respiratory distress syndrome, genetic research, SFTPB, SFTPC, ABCA3.

INTRODUCTION

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Respiratory distress syndrome (RDS) is a respiratory disorder in newborns that manifests immediately after birth and is one of the most common causes of admission to neonatal intensive care units and respiratory failure (1). Factors contributing to the development of RDS include maladaptation, delayed adaptation, congenital anomalies, and acquired infections (2). The prevalence of RDS among newborns is 18.5% in France (3), 4.24% in Pakistan (4), and 20.5% in China (5). RDS also occurs in full-term infants, accounting for 6.8% of cases (7). Another study found that 48 out of 1986 newborns (2.42%) developed RDS, of which 7 (14.6%) weighed more than 2500 grams (8). Registered risk factors for RDS include male gender, cesarean section, maternal diseases (hypertension, diabetes), chorioamnionitis, and multiple pregnancies (10, 11, 12). The prognosis of RDS depends on the severity and underlying cause (5). In China, a mortality rate of 3.9% was reported among full-term infants with RDS (12). The incidence of RDS among full-term newborns was 1.64%, with higher rates reported in India (4.2%) (13), Turkey (7%) (14), and Sudan (4.83%) (15). A prospective multicenter study in Italy showed a lower incidence of RDS (1.16%) in full-term newborns (16). Artificial conception is also associated with an increased risk of RDS.

Recognizing risk factors for RDS is crucial for developing preventive and early treatment strategies (18). While the RDS group had more cases of cesarean section and PROM, this did not reach statistical significance. The association between cesarean section and RDS has been confirmed in previous studies (19). Gouyon JB et al. (20) established that elective cesarean section is a major risk factor for RDS in full-term infants. Fetal growth restriction (FGR) requires a unified approach for early recognition and management to improve antenatal and postnatal outcomes. FGR management mainly focuses on the timing and mode of delivery, with an emphasis on continuous fetal heart rate monitoring and placental histopathological examination (21). Managing pregnancies complicated by FGR or small for gestational age (SGA) fetuses requires standardized approaches and further research to improve outcomes (22). Twin pregnancies are associated with a high risk of complications, and recommendations from various professional societies often diverge, highlighting the need for international consensus (23, 24). Premature births occur more frequently via cesarean section, with early gestational age being the main factor for neonatal morbidity and mortality, while the mode of delivery does not affect neonatal survival (25). Vaginal delivery in severe preterm births is associated with an increased risk of neonatal and perinatal mortality in breech presentation fetuses (26).

The onset of spontaneous labor promotes the rapid clearance of fetal lung fluid and lung maturation (27). Antenatal corticosteroids for women at risk of preterm labor reduce the risk of moderate and severe RDS (28). In our study, infants with RDS had lower birth weights

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and lower Apgar scores (29). The mortality rate among full-term infants with RDS was 5.1%, which may be associated with the widespread use of oxygen and continuous positive airway pressure (CPAP) (13, 30). Some risk factors affect the incidence of RDS differently at different gestational ages (31).

Identifying genetic mutations and polymorphisms associated with RDS will allow the development of more rational treatment strategies and accurate counseling for families whose children are at risk (32). The incidence of RDS in preterm infants is 45% at 23-33 weeks of gestation, decreasing to 4% at 34-36 weeks and less than 1% at over 37 weeks. In Korea, the incidence of RDS in full-term infants was more often observed in males (OR 3.288), with cesarean section (OR 15.03), and multiple pregnancies (OR 4.216) (33).

RDS often arises from a deficiency of surfactant, which is synthesized by type II alveolocytes. Surfactant consists of lipids and proteins (SP-A, SP-B, SP-C, SP-D). Mutations in the genes encoding these proteins (SFTPB, SFTPC, ABCA3) can lead to surfactant dysfunction and RDS. For example, the SFTPB mutation, 121ins2, accounts for more than half of all cases of SP-B deficiency, inherited in an autosomal recessive manner. SP-C deficiency is inherited in an autosomal dominant manner, and ABCA3 mutations are a major cause of congenital surfactant dysfunction. In a retrospective analysis of 332 twin pairs, a mixed-effects logistic regression analysis (MELR) was used to assess the influence of various factors on RDS. Male gender, birth weight, 5-minute Apgar score, and treatment site were significant covariates. ACE analysis showed that 49.7% of the variability in RDS susceptibility is due to genetic factors (34).

Inherited SP-B deficiency is a rare cause of respiratory failure in full-term newborns. Homozygosity for the SFTPB mutation (1549C->GAA or 121ins2) leads to fatal respiratory failure with the absence of SP-B mRNA and protein. SP-B deficiency is also associated with abnormal processing of proSP-C and a deficiency of active SP-C peptide (35).

Pulmonary surfactant protein A (SP-A) plays a key role in lung protection and surfactant function. The genetic complexity of SP-A has increased during evolution, especially in regulatory regions. Most species have one SP-A gene, but humans and primates have two genes (SFTPA1 and SFTPA2). SP-A expression regulation involves transcription, splicing, mRNA degradation, and translation. This report aims to describe the genetic complexity of the SFTPA1 and SFTPA2 genes and review the regulatory mechanisms controlling their expression (36).

Pulmonary surfactant, a lipoprotein complex, maintains alveolar integrity and plays an important role in lung protection and inflammation control. Genetic variants of surfactant proteins, including single nucleotide polymorphisms (SNPs), haplotypes, and other variations, have been associated with acute and chronic lung diseases. Hydrophilic surfactant proteins SP-A and SP-D, also known as collectins, play an

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important role in innate immunity by binding to pathogens and allergens and promoting their clearance. A review of studies links genetic polymorphisms of surfactant proteins A and D with respiratory and non-respiratory diseases in adults, children, and newborns (37).

Case-control groups showed significant differences in genotype and allele frequencies of SP-A (+186A/G, +655C/T) and SP-B (1580C/T), indicating an association of these polymorphisms with the risk of RDS in preterm infants. Decreased serum SP-A levels may serve as new biomarkers for the detection and monitoring of RDS (38).

The frequencies of SP-A1 6A2 and 6A3 alleles were low, while SP-A2 1A0 and 1A1 alleles were high in normal preterm Chinese infants. The SP-A1 6A2 allele may be a susceptibility gene for RDS (39). The SP-B 1580C/T polymorphism contributes to the etiology of RDS, while SP-B -18A/C shows no significant association (41). Specific genetic variants of SP-A may affect the susceptibility to RDS in preterm infants, independent of other perinatal factors (43). RDS is caused by lung immaturity and a temporary deficiency of alveolar surfactant. Genetic predisposition to RDS varies depending on the degree of prematurity. Genetic variability in the SP-A and SP-B genes is associated with susceptibility to RDS, while rare mutations in SP-B and SP-C cause severe lung disease. Genetic studies may lead to new diagnostic and therapeutic approaches for preventing respiratory failure and inflammatory lung diseases (44, 45).

Unlike lethal neonatal RDS caused by homozygous ABCA3 mutations, individual ABCA3 mutations account for ~10.9% of the attributable risk among full-term and late preterm infants of European descent. These mutations are prevalent among individuals of European and African descent in the general population (46). Rare or novel genetic variants in the genes encoding surfactant proteins were identified in 35% of preterm infants with severe RDS, indicating possible interaction between genetic and developmental factors (47). Mutations in the genes encoding surfactant proteins B and C (SP-B and SP-C) and the phospholipid transporter ABCA3 are associated with respiratory distress and interstitial lung disease. The expression of these proteins increases with gestational age and is crucial for surfactant function. SP-B and ABCA3 are necessary for packaging surfactant phospholipids, while SP-B and SP-C are important for surfactant adsorption on the alveolar surface. SFTPB mutations are associated with fatal neonatal RDS, while SFTPC mutations are linked to interstitial lung disease in infants, children, and adults (48).

Congenital surfactant deficiency (CSD) is a neonatal disease associated with defects in the synthesis and secretion of surfactant in type II alveolar cells. Abnormal lamellar bodies were identified in four infants with CSD. Two had SP-B deficiency, and two had

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ABCA3 mutations. Transmission electron microscopy (TEM) revealed the absence of mature lamellar bodies and the presence of electron-dense inclusions, highlighting the importance of TEM for CSD diagnosis (49, 50).

Heterozygous SFTPC mutations are associated with interstitial lung disease (pILD) in adults and children. ABCA3 mutations also cause pILD and can modify disease severity in patients with SFTPC mutations (52). SFTPC mutations lead to various manifestations and outcomes. For example, the c.435G->A mutation is associated with early symptom onset and severe respiratory failure requiring lung transplantation (53). SFTPC mutations can also alter surfactant protein trafficking and processing, affecting clinical manifestations (54).

SFTPC mutations and other genetic factors play a significant role in the development and manifestation of pediatric interstitial lung diseases. Genetic testing is essential for diagnosing such diseases (55-60). Knowledge of airway anomalies and their association with genetic mutations is crucial for the correct diagnosis and treatment of respiratory distress in newborns (61, 62). Among 17 children from 16 families with mutations in the SFTPC, ABCA3, and NKX2-1 genes, congenital deficiency of surfactant protein C, brain-lung-thyroid syndrome (BLTS), and congenital ABCA3 protein deficiency were observed. The lethality rate for surfactant protein C deficiency was 37.5%. Genetic testing is necessary for children with severe respiratory distress syndrome and a family history, as well as in cases where respiratory symptoms are combined with congenital hypothyroidism and neurological pathology (63, 64, 65, 66).

The risk of respiratory disorders in newborn boys carrying the 2A allele and the 1A2A genotype of the T3801C polymorphic locus of the CYP1A1 gene is twice as high. The 1A1F genotype of the C-163A polymorphic locus of the CYP1A2 gene is a marker for the risk of RDS complicated by pneumonia (67). A study of 130 pregnancies with FGR and structural malformations showed that 28.5% of cases had chromosomal abnormalities. Using SNP arrays and CMV DNA testing in FGR cases can improve pregnancy diagnosis and management (68, 69, 70). Genetic variation in LPCAT1 may be involved in the pathophysiology of RDS in preterm infants of the Han Chinese population. The GG genotype and G allele of rs9728 are protective factors for RDS development (71). The NK2 homeobox-1 gene (NKX2.1) is associated with the morphogenesis and function of the lungs, thyroid, and CNS. Mutations cause a rare form of progressive respiratory failure known as brain-lung-thyroid syndrome. Deletions at 14q13.3 adjacent to NKX2-1 can cause various symptoms, including choreoathetosis, congenital hypothyroidism, and respiratory distress syndrome. Genetic testing is important for diagnosing and managing these diseases (72-76).

Thus, the role of genetic defects in the development of neonatal RDS is an important aspect in understanding

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the pathophysiology of the disease. Genetic polymorphisms and mutations in surfactant protein genes significantly influence susceptibility to RDS and can be used to improve diagnosis, prevention, and treatment of this serious condition.

CONCLUSIONS

1. Risk factors for full-term newborns include male gender, cesarean section, and multiple pregnancies. Early diagnosis and treatment are necessary to prevent complications.
2. Genetic mutations in the SFTPB, SFTPC, and ABCA3 genes encoding surfactant proteins can lead to RDS and interstitial lung diseases with various clinical manifestations.
3. Genetic variability in surfactant protein genes and transporters, such as ABCA3, may enhance the effect of immature surfactant production, worsening the course of RDS.
4. The molecular mechanisms of RDS are associated with surfactant deficiency, disrupting its function and leading to respiratory disorders.
5. Transcription factors and genes regulating surfactant protein expression are important for lung development and function and are candidates for research on new treatments for RDS.
6. Population genetic studies will help understand the contribution of genetic mutations to the incidence of RDS and other lung diseases, improving treatment strategies and genetic counseling.

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