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Predictive role of neurotrophic markers in intrauterine infections

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ABSTRACT

Preterm birth is a major risk factor for neurodevelopmental delays and disorders. This study aimed to identify genomic biomarkers of intrauterine inflammation in umbilical cord tissue in preterm neonates that predict cognitive impairment at 10 years of age. Genome-wide messenger RNA (mRNA) levels from umbilical cord tissue were obtained from 43 neonates born before 28 weeks of gestation. Genes that were differentially expressed across four indicators of intrauterine inflammation were identified and their functions examined. Exact logistic regression was used to test whether expression levels in umbilical cord tissue predicted neurocognitive function at 10 years of age. Placental indicators of inflammation were associated with changes in the mRNA expression of 445 genes in umbilical cord tissue. Transcripts with decreased expression showed significant enrichment for biological signaling processes related to neuronal development and growth. The altered expression of six genes was found to predict neurocognitive impairment when children were 10 years old These genes include two that encode for proteins involved in neuronal development. Prenatal intrauterine inflammation is associated with altered gene expression in umbilical cord tissue. A set of six of the differentially expressed genes predict cognitive impairment later in life, suggesting that the fetal environment is associated with significant adverse effects on neurodevelopment that persist into later childhood.

1. Introduction

Preterm birth, defined as delivery at < 37 completed weeks gestation, is currently the leading cause of neonatal morbidity and mortality in the United States [1]. Individuals born prematurely are at increased risk for other adverse health outcomes, and those born at less than 28 weeks gestation are at particularly high risk [2]. Perhaps most important are adverse neurodevelopmental outcomes, which affect an estimated 1 million preterm infants born each year [3]. Preterm birth is thought to be caused by the pathological induction of certain components of the normal parturition process resulting from a combination of environmental, genetic, and behavioral factors [4], [5]. Many identified risk factors have the potential to promote inflammatory processes [6]. Indicators of intrauterine inflammation are present in as many as 40–70% of preterm births, versus only 1–13% of full term births [7]. These data support the hypothesis that risk

of preterm birth is increased by pathological, environmental, and/or genetic factors that contribute to delivery-inducing inflammation [4], [8]. Among preterm infants, biomarkers of prenatal inflammation, including inflammatory cytokines in amniotic fluid [9], placental histologic findings [10– 12], and inflammation-related proteins in neonatal blood [13– 17], are associated with a range of neurodevelopmental impairments [18]. A fetal inflammatory response (FIR) is associated with increased expression of a broad array of genes related to neurodevelopment [19]. In the present study, we aimed to identify whether genomic signaling changes in umbilical cord tissue were associated with a suite of four histologic markers of prenatal inflammation in a subset of infants from the Extremely Low Gestational Age Newborns (ELGAN) cohort. We hypothesized that some of these genomic changes would be predictive of neurocognitive function at 10 years of age and could provide novel predictive biomarkers of neurocognitive impairment in preterm infants.

2. Case presentation

A 45-year-old woman was admitted to our department with a 5-day history of abdominal distention and dull pain, especially at the upper umbilical region, and vomiting of gastric content without passage of stools or flatus. She had an erect abdominal plain radiograph which showed intestinal obstruction in a local hospital previously. A careful medical history was taken on admission. Three years ago, she suffered from cervical cancer and had a radical hysterectomy with adnexectomy. The postoperative pathological diagnosis is cervical moderately differentiated squamous cell carcinoma with its maximum diameter to 9 mm and infiltration depth to 2 mm. No lymph node metastasis was found in the bilateral pelvic and common iliac lymph node. It was diagnosed with International Federation of Gynecology and Obstetrics (FIGO) stage IB1 cervical cancer. After the operation, she had a 3- to 6-month follow-up but did not have any radiotherapy or chemotherapy.

3. Discussion

In this study, we have demonstrated evidence of genomic signaling changes in the umbilical cord tissue of extremely preterm infants that are associated with multiple markers of intrauterine inflammation. Two interesting patterns of gene expression were observed; inflammationassociated genes displayed increased expression in the cord, while among the genes that displayed decreased expression, several were related to neurodevelopment. Expression levels of six genes altered in umbilical cord tissue in association with one or more intrauterine inflammation marker significantly predict the risk of neurocognitive impairment later in life. In support of our data, several of these genes whose decreased expression predicted more severe cognitive impairment have been previously implicated in neuronal development. Our results indicate that genomic changes observable at parturition in the umbilical cord tissue of extremely low gestational age newborns are associated with neurocognitive function later in life. Preterm newborns are at increased risk for numerous adverse health effects, many of which are related to prenatal intrauterine inflammation, including neurodevelopmental impairment.

4. Conclusions

This report presents a rare case of small intestine and sigmoid colon metastases of cervical cancer that caused obstruction. Clinicians should be aware that intestine metastasis must be considered in the differential diagnosis of acute abdomen in patients with cervical cancer even at an early tumor stage.

5. References

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