News and Views

Integrating Diabetes and Cognitive Care

Diabetes is strongly associated with a faster rate of cognitive decline in patients with mild cognitive impairment (MCI). This decline was most pronounced within the first year of diagnosis. Also, patients with diabetes had a higher likelihood of progressing from MCI to Alzheimer's disease (AD) compared to those without diabetes. Diabetes mellitus also negatively affects brain areas involved in cognitive functioning. These findings were published online June 12, 2024 in the journal *Alzheimer's & Dementia*[1].

This study used the Alzheimer's Disease Neuroimaging Initiative dataset to determine the optimal time window to intervene to slow or prevent the transition from MCI to AD as well as to identify the neurobiological targets that could be targeted to prevent or slow down the progression from MCI to AD. A total of 980 participants diagnosed with MCI were included in the study were categorized based on their diabetes status. They underwent neuroimaging and cognitive evaluation to assess the rate of conversion from MCI to AD, neuroimaging changes and cognitive changes. One hundred-two diabetes patients were matched with 2 patients without diabetes (n = 204).

A strong correlation between diabetes and cognitive deterioration as well as an elevated risk of AD progression, particularly during the first year of MCI follow-up was observed. It has a negative impact on several brain regions, most notably on the nucleus accumbens where it hastened significant atrophy and a decrease in the gray matter volume and sulcal depth.

Researchers found no statistically significant difference in conversion to AD between patients with and without diabetes over the follow-up period of 11 years. Nonetheless, more diabetic patients (8.82%) progressed to AD within the first 12 months following the diagnosis of MCI than those without DM (2.45%). According to absolute differences in the Participant-reported Everyday Cognition Scale Plan (EcogPtPlan), Rey's Auditory Verbal Learning Test immediate recall (RAVLT-immediate), Alzheimer's Disease Assessment Scale task 4 (ADASQ4) and relative differences in RAVLT-immediate outcomes, patients with diabetes mellitus were found to have worse cognitive impairment at year 1 relative to baseline compared to those who did not have diabetes.

Compared to the subjects without diabetes mellitus, patients with diabetes had a marked inwardly concave surface and mild atrophy of the left nucleus accumbens at the start of the study. At 12 months, atrophy of the left nucleus accumbens was found to persist. Additionally, they also displayed atrophy in the right nucleus accumbens. Over the follow-up period, patients with diabetes also had changes in cortical thickness and gyrification index along with decreased sulcal depth.

These findings highlight the first year following the diagnosis of MCI in patients with diabetes as a crucial window for therapeutic intervention. Early and aggressive diabetes care in patients with MCI with regular cognitive assessments and monitoring are essential to detect and address changes promptly. This includes implementing lifestyle changes such as diet and exercise together with maintaining blood sugar levels and managing comorbid conditions to mitigate the impact of diabetes on cognitive health. Further, understanding the specific brain structures affected by diabetes mellitus can guide the development of targeted neuroprotective therapies.

Reference

1. Ding X, et al; Alzheimer's Disease Neuroimaging Initiative. Diabetes accelerates Alzheimer's disease progression in the first year post mild cognitive impairment diagnosis. Alzheimers Dement. 2024 Jun 12. doi: 10.1002/alz.13882.

Predicting Respiratory Morbidity after Early-Life RSV Infection

Lower gestational age and age at first respiratory syncytial virus (RSV) infection are linked to a higher incidence of subsequent respiratory morbidity following early-life RSV infection, according to a study published in the journal *Open Forum Infectious Diseases*[1]. Maternal history of asthma and low socioeconomic status were also associated with later respiratory morbidity.

For this study, the investigators employed a whole-of-population birth cohort that was probabilistically linked, and consisted of 2,52,287 children born in Western Australia between 2000 and 2009, and was examined up to the end of 2012. The associations between different risk factors and the first respiratory episode of asthma, wheezing, and an unspecified acute lower respiratory infection after the age of 2 years. The study also examined

the prenatal and sociodemographic characteristics linked to respiratory illness in later childhood that required secondary treatment after exposure to an RSV episode that was confirmed in the laboratory during the first 2 years of life.

A total of 4,151 children who had a confirmed RSV test before the age of 2 years were included in the analysis.

The highest incidence of subsequent respiratory morbidity following early-life RSV infection was observed in children aged 2 to <4 years, with an incidence rate of 41.8 per 1,000 child-years. The incidence of respiratory morbidity increased with the age at which the child was infected with RSV. For children infected at the age of 6 to <12 months, the incidence rate was 23.6 per 1,000 child-years. For children infected at 12 to <24 months age, the incidence rate was 22.4 per 1,000 child-years.

The incidence of respiratory morbidity decreased with gestational age. The incidence rate was 50.8 per 1,000 child-years among children who were born extremely premature (<28 weeks gestation).

The study also identified several risk factors for subsequent respiratory morbidity following an early-life RSV infection. Children who experienced their first RSV episode between 6 to <12 months of age had a higher risk of subsequent respiratory morbidity with adjusted hazard ratio (aHR) of 1.42. Children born extremely premature (<28 weeks gestation) and those with maternal history of asthma were at a significantly higher risk with aHRs of 2.22 and 1.33, respectively. Low socioeconomic index was another significant risk factor (aHR 1.76).

This study therefore suggests that the recommendations for RSV prevention such as vaccination can be extended beyond preterm and very young infants to also include older children, between the ages of 12 and <24 months, in order to lessen the burden of subsequent respiratory morbidities linked to RSV. Parents should be educated about the importance of RSV prevention in children up to 24 months old.

Reference

1. Sarna M, et al. Factors predicting secondary respiratory morbidity following early-life respiratory syncytial virus infections: population-based cohort study. Open Forum Infect Dis. 2023;10(10):ofad450.

Long-term Safety of Metformin Use in Pregnancy

Use of metformin to treat gestational diabetes or diabetes during pregnancy did not have any negative impact on the long-term outcomes for both children and mothers, according to the results of a study recently published online June 12, 2024 in the journal *Endocrine Practice*[1]. Exposure to metformin did not adversely affect the metabolic health or development of children, 5 to 11 years of age, compared to insulin exposure. It also did not increase the risk of adverse metabolic outcomes postpartum in mothers.

The study designed as a meta-analysis and systematic review undertook to assess the long-term effects of metformin use during pregnancy on mothers and their offspring at the age of 9 years compared to insulin use. Relevant studies comparing metformin against insulin for the treatment of gestational diabetes mellitus or diabetes were identified following a comprehensive search of several electronic databases. Seven randomized controlled trials and cohort studies were included in the final analysis. Any change in the body mass index (BMI) in children at 5 and 11 years of age was the primary study endpoint. The secondary outcomes were the changes in other anthropometric parameters, obesity prevalence, and metabolic parameters (lipids and adipocytokines) in mothers and children.

At 9 years of age, no significant difference was observed in BMI between children whose mothers were treated with metformin and those treated with insulin. The mean difference (MD) was 1.09 kg/m^2. They also had comparable waist circumference-to-height ratio (MD 0.13), total fat mass measured by dual-energy X-ray absorptiometry (MD 0.68 kg) and total fat percent (MD 0.04%), total fat-free mass (MD 0.81 kg), visceral adipose tissue volume (MD 80.97 cm^3), and liver fat percentage (MD 0.27%).

The levels of ferritin, alanine aminotransferase, leptin, and serum adiponectin were similar between the two groups. The prevalence of obesity, diabetes, or difficulties with motor and social development in children between the ages of 9 and 11 years did not show any significant difference between the two groups. Showing a similar trend, no differences in BMI or the risk of developing diabetes in mothers were observed between metformin and insulin groups at 9 years postpartum.

This meta-analysis has for the first time analyzed the long-term outcomes of use of metformin vis-a-vis insulin during pregnancy. Metformin was as safe as insulin for the treatment of gestational diabetes or diabetes during pregnancy, with no significant differences in the long-term health of both mothers or the infants. The ease of administration and positive metabolic effects further reinforce the potential benefits of metformin use during pregnancy. Hence, metformin may be considered as

a safe and effective alternative to insulin. However, further research is needed to elucidate on outcomes into adulthood.

Reference

1. Dutta D, et al. Long-term impact on offspring (5 to 11 years of age) of metformin use in pregnancy in mothers with diabetes: a systematic review and meta-analysis. Endocr Pract. 2024 Jun 12:S1530-891X(24)00559-7.

Predisposing Factors for Pneumomediastinum in COVID-19 Pneumonia Patients

Although the COVID-19 pandemic has officially ended, there are still many unknowns about the virus and its impact. Ongoing research continues to delve into various aspects of the disease to enhance our understanding and improve future responses to public health challenges of such nature.

Adding to the growing evidence, a team of researchers from Italy undertook a multicenter case-control study to identify risk factors for COVID-19-associated pneumomediastinum and to also investigate its impact on the clinical outcomes of patients[1]. Patients hospitalized with COVID-19 pneumonia and pneumomediastinum from March 2020 to July 2020 at 10 centers were included in the study. Another group of inpatients with COVID-19 pneumonia and respiratory failure who did not develop pneumomediastinum during the same period were also included as controls. Data were gathered and compared between the two groups for respiratory support, radiologic features, laboratory findings, clinical characteristics, and clinical outcomes.

The analysis was performed on a cohort of 139 patients with pneumomediastinum and 153 patients without pneumomediastinum.

Results published in the journal *Respiratory Medicine* show that pneumomediastinum was independently linked with lung involvement of ≥75%, presence of consolidation, BMI <22 kg/m^2, C-reactive protein (CRP) >150 mg/L, D-dimer >3,000 ng/mL fibrinogen equivalent units, and smoking exposure of >20 pack-years.

Over half of the patients (52.5%) with pneumomediastinum required intubation compared to 17.6% patients in the control group. Likewise, pneumomediastinum patients had higher rates of in-hospital mortality (48.9% vs. 23.5%) along with longer mean duration of hospitalization (31.2 days vs. 19.6 days) versus controls.

The study has identified various risk factors for the development of pneumomediastinum in patients with COVID-19 pneumonia. These include extensive lung involvement, presence of consolidation, low BMI, elevated inflammatory markers (CRP and D-dimer) and significant smoking history. Patients with these risk factors have worse clinical outcomes with regard to in-hospital mortality and duration of hospitalization. Clinicians should be vigilant in identifying patients at higher risk for pneumomediastinum based on the identified risk factors. The high-risk patients may benefit from enhanced monitoring and early intervention to mitigate the impact of pneumomediastinum. Hence, there is the need for adoption of strategies to mitigate severe lung involvement and control inflammation in patients with COVID-19 pneumonia.

Reference

1. Negri S, et al. Pneumomediastinum in COVID-19: Risk factors and outcomes from a multicentre case-control study. Respir Med. 2024;230:107684.

Timely Antibiotic Administration Mitigates Mortality Risk in Pediatric Sepsis

Administration of antibiotics at 330 minutes or later (>5.5 hours) to children with sepsis presenting to the emergency department (ED) is associated with more than threefold increase in mortality at 3 days and 30 days, according to findings of a study from the US published in *JAMA Network Open*[1].

Data from 51 children's hospitals in the US participating in the Improving Pediatric Sepsis Outcomes collaborative was analyzed for this multicenter, retrospective cohort study. Patients diagnosed with sepsis within an hour of arriving at the emergency room from January 2017 to December 2021 were included. Their ages ranged from 29 days to <18 years.

The period of data analysis was March 2022 to February 2024. The objective of the study was to identify a critical time point at which antibiotic administration was linked to a higher risk of death in children with sepsis. The main outcome of the study was 3-day mortality due to sepsis. The secondary endpoint was 30-day death attributable to sepsis.

This retrospective cohort study included a total of 19,515 pediatric cases with sepsis, with a median age of 6 years. The median time before antibiotics were administered was 69 minutes. The results showed that the estimated median time to antibiotic administration, which resulted in an increase in 3-day sepsis-related mortality was 330 minutes (5.5 hours). For every increase of 30 minutes beyond this cut-off point, the risk of mortality significantly increased with odds ratio (OR) of 2.44.

A total of 19,164 patients received an antibiotic in <330 minutes. Of these, 93 patients had a sepsis-related 3-day mortality of 0.5%, while 163 patients had a 30-day mortality of 0.9%.

The 3-day mortality due to sepsis in those who received antibiotics at 330 minutes or later was 1.2% (vs. 0.5%). The 30-day mortality rate was 2.0% (vs. 0.9%) in the delayed treatment group.

In adjusted analysis, those who received antibiotics at or any time after 330 minutes (351 patients) had higher adjusted odds of sepsis-attributable mortality at 3 days (OR 3.44) and 30 days (OR 3.63) compared with antibiotics given before 330 minutes.

The presence of bacteremia (aOR 2.78), lactate levels above 36 mg/dL (aOR 9.38), IPSO-defined critical sepsis (aOR 5.06), the existence of high-risk conditions (aOR 2.29), and receiving long-term ventilation (aOR 2.13), were among the factors associated with an increased risk of sepsis-attributable mortality at 3 and 30 days.

This study demonstrates significant differences in the adjusted odds of sepsis-related mortality based on the timing of antibiotic administration in pediatric patients with sepsis. These findings align with existing literature and guidelines, which highlight that delay in antibiotic treatment are associated with adverse outcomes in cases of pediatric sepsis. Hence, these conclusions underscore the critical importance of timely antibiotic treatment in improving outcomes in this high-risk group of patients.

Reference

1. Lane RD, et al. Delays to antibiotics in the emergency department and risk of mortality in children with sepsis. JAMA Netw Open. 2024;7(6):e2413955.

Outcomes in Pregnancy with Uterine Fibroids

The size of the uterine fibroids, and not their number, increases the risks for adverse pregnancy and obstetric outcomes including breech presentation, postpartum hemorrhage (PPH), and placenta previa, according to a recent study published in the journal *BMC Pregnancy and Childbirth*[1].

This meta-analysis was conducted to ascertain the impact of uterine fibroids on adverse consequences, with particular focus on the multiple or big fibroids measuring ≥5 cm in size. Li and colleagues looked through the databases of PubMed, Embase, Web of Science, ClinicalTrials.gov, China National Knowledge Infrastructure (CNKI), and SinoMed to find relevant research on the impact of uterine fibroids on unfavorable pregnancy outcomes. Twenty-four studies with a total of 2,37,509 participants were included in the analysis.

Pooled analysis revealed that uterine fibroids significantly increased the risks of a number of unfavorable pregnancy and obstetric outcomes, such as low birth weight (relative risk [RR] 1.72), breech presentation (RR 2.26), preterm birth (RR 1.72), placenta previa (RR 2.99), miscarriage (RR 4.51), preterm premature rupture of membranes (PPROM) (RR 1.37), placental abruption (RR 1.85), PPH (RR 3.52), and fetal distress (RR 3.61).

Adverse effects, however, were only observed for preterm birth, cesarean delivery, placenta previa, placental abruption, PPH, intrauterine fetal mortality, breech presentation, and pre-eclampsia after correcting for the potential confounding factors.

A subgroup analysis further revealed that compared to smaller fibroids (<5 cm), larger fibroids (>5 cm) significantly increased the risks for PPH (RR 5.04), breech presentation (RR 1.5), and placenta previa (RR 1.62).

The risk of breech presentation, placental abruption, cesarean delivery, PPH, placenta previa, PPROM, preterm birth, and intrauterine growth restriction (IUGR) was not increased by the presence of multiple fibroids. On meta-regression analysis, the relationship between uterine fibroids and intrauterine fetal death was influenced by BMI, while the association between uterine fibroids and preterm birth was solely impacted by the age of the mother. Outcomes such as malposition, fetal discomfort, placenta previa, placental abruption, PPROM, miscarriage, and PPH were unaffected by other potential confounding factors.

These findings highlight the importance of considering individual factors like maternal age and BMI when assessing the risks associated with uterine fibroids in pregnancy. This helps in managing and counseling patients with uterine fibroids during pregnancy to diminish the impact of these risks. "Our results provide valuable information for the identification of the risks of breech presentation, PPH, and placenta previa," write the authors.

Reference

1. Li H, et al. The influence of uterine fibroids on adverse outcomes in pregnant women: a meta-analysis. BMC Pregnancy Childbirth. 2024;24(1):345.

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