Clinical pathology selected abstracts

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Trends in postmortem neurodegenerative and cerebrovascular neuropathologies

June 2023—Studies that address whether the incidence of dementia in the U.S. population is declining are inconsistent. They cannot establish conclusive trends in disease rates. Most studies are hard to interpret due to small sample sizes or use of hospital-based autopsies. Understanding trends in dementia is necessary from a public health perspective and for planning interventions. Therefore, the authors conducted a study to characterize trends in pathways underlying dementia using two U.S. cohorts focused on aging and dementia. The study affords an opportunity to observe trends in neuropathology specifically focused on clinical dementia. It characterizes the trends in pathways underlying dementia by examining the prevalence of postmortem neuropathology in birth cohorts across 25 years. The authors used two longitudinal cohorts—the Religious Orders Study and the Rush Memory and Aging Project—and reviewed autopsy data from 1997 to 2022 for the main outcomes of pathologic diagnosis of Alzheimer's disease (AD), global AD pathology, amyloid load, tau tangles, neocortical Lewy bodies, limbic-predominant age-related TDP-43 encephalopathy neuropathological change, atherosclerosis, arteriolosclerosis, gross chronic infarcts, and chronic microinfarcts. Four categories of years of birth—1905 to 1914, 1915 to 1919, 1920 to 1924, and 1925 to 1930—served as cohorts for the population analysis. Pathologies in each category of birth years were standardized to the age distribution of the cohorts, and X^2 tests were used for outcomes. Analysis of variance was used to compare means across the birth cohorts. The authors studied 1,350 participants using autopsies and complete neuropathological assessments for clinical dementia-related outcomes. (They excluded from the study those subjects born before 1905 or after 1930 because their ages at death did not adequately overlap other birth epochs, as well as those whose last clinical evaluation was more than two years before their death.) The results showed that participants were distributed evenly across birth cohorts. No differences in prevalence of pathologic AD diagnosis were found across year-of-birth groups. Age-standardized prevalence fluctuated between 62 percent and 68 percent in the birth cohorts. Similarly, no differences in mean levels of global AD pathology were found, although a greater density of tau tangles in later birth cohorts was noted. No differences in other neurodegenerative pathologies were reported, but atherosclerosis and arteriosclerosis were dramatically lower over time for those born between 1905 and 1915 (54 percent) versus those born between 1925 and 1930 (22 percent). The authors concluded that this study demonstrated only a few differences in neurodegenerative pathologies but worse levels of tau tangles across birth cohorts over 25 years. They suggested that this indicates improved resilience to pathology rather than overall reduced AD pathology. In contrast, the authors showed a marked difference over time in atherosclerosis and arteriosclerosis, consistent with the national trend of decreasing vascular morbidity in older people.

Grodstein F, Leurgans SE, Capuano AW, et al. Trends in postmortem neurodegenerative and cerebrovascular neuropathologies over 25 years. *JAMA Neurol*. 2023. doi:10.1001/jamaneurol.2022.5416

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Monitoring DTIs in pediatric patients using diluted thrombin time versus aPTT

Administration of the intravenous direct thrombin inhibitors argatroban and bivalirudin to pediatric and adult patients has increased significantly in recent decades. Their use has expanded beyond patients with heparin-induced thrombocytopenia (HIT) to cardiac patients. Intravenous direct thrombin inhibitors (DTIs) have been reported to improve outcomes for patients on extracorporeal life support or who have ventricular-assist devices, as well as for those who had a myocardial infarction and are undergoing percutaneous coronary intervention.

However, use of DTIs has been hampered by the availability of accurate monitoring assays that correlate with therapeutic effect. Activated partial thromboplastin time (aPTT) assays are used in many settings to monitor the efficacy of DTI, but the accuracy of aPTT is reduced at higher DTI concentrations, which creates a plateau effect despite increased dosing. Furthermore, baseline aPTTs are often elevated in patients who have factor deficiencies, liver dysfunction, and lupus anticoagulants. An alternative test, the plasma diluted thrombin time (dTT) assay, has been shown to correlate more closely with DTI levels than aPTT. The authors conducted a study to compare dose-response curves for dTT and aPTT in pediatric patients receiving argatroban or bivalirudin. A secondary aim of the study was to compare the differences in dose response for argatroban and bivalirudin. The authors performed a retrospective review of pediatric patients treated with argatroban (n=45) or bivalirudin (n=14) who were monitored with dTT and aPTT. They collected data on paired argatroban dose, argatroban level, and aPTT from patients who had been taking argatroban at a fixed dose for at least four hours. They also collected data on paired bivalirudin dose, bivalirudin level, and aPTT from patients who had been taking bivalirudin at a fixed dose for at least two hours. Both the calibrated argatroban and bivalirudin level assays were laboratory-developed tests. The testing showed good analytic sensitivity and specificity. The results indicated that dTT was five times more likely to demonstrate a stable dose-response slope than aPTT ($P<.0002$; odds ratio, 4.9). For the patients in whom both dTT and aPTT showed a significant correlation with dose and assay results, dTT had a higher average correlation than aPTT ($P=.007$). Furthermore, argatroban dose-response slopes showed more variation between patients compared with bivalirudin. The authors concluded that the dTT assay is more likely to demonstrate a stable dose response and a stronger correlation with DTI dose than aPTT.

Hasan RA, Pak J, Jefferis C, et al. Monitoring direct thrombin inhibitors with calibrated diluted thrombin time vs activated partial thromboplastin time in pediatric patients. *Am J Clin Pathol*. 2023;159:60–68.

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