

QoL was measured in 1,268 patients (45% female) at 180 days after treatment randomization, using the Short Form-36 health survey. The mean age of female patients was significantly greater than that of male patients (73.4 years vs 68.4 years;  $P < 0.0001$ ). In addition, female patients were more likely to have atrial fibrillation, to have a lower premorbid functional status (as measured by the modified Rankin Scale [mRS]), and to be in a nursing home, than were male patients.

Overall, QoL scores for female patients were markedly lower than those for male patients; female patients scored particularly poorly on the domains relating to physical functioning, vitality and mental health. Even following adjustment for age, baseline systolic blood pressure, Scandinavian Stroke Scale score, history of myocardial infarction, stroke type, premorbid mRS score, premorbid residency (home/nursing home), and treatment group, female patients had considerably lower scores for physical functioning and mental health than did male patients. Notably, lower scores on the physical functioning and mental health QoL domains were associated with poor functional outcome at 6 months, as assessed by the mRS ( $P < 0.0001$  for both).

**Original article** Gray LJ *et al.* (2007) Sex differences in quality of life in stroke survivors: data from the Tinzaparin in Acute Ischaemic Stroke Trial (TAIST). *Stroke* 38: 2960–2964

## Blood plasma biomarkers could predict Alzheimer's disease

Early and definitive diagnosis of Alzheimer's disease (AD) could lead to better and more-targeted treatment for patients. Ray *et al.* have recently identified a group of plasma signaling proteins that reflect changes in the brain during the early stages of AD pathology. Levels of the 18 proteins in blood plasma can be used to identify patients with AD, or to predict the onset of AD in presymptomatic patients, with close to 90% accuracy.

First, the authors measured the relative abundance of 120 signaling proteins in an initial set of samples from 43 patients with AD and 40 controls without dementia, and through statistical analysis found significantly different expression patterns of 19 proteins ( $q$ -value  $< 3.4\%$ ), from which a set of 18 predictors of AD was

identified. When the predictors were then tested in independent samples from patients with AD ( $n = 42$ ) and other types of dementia ( $n = 11$ ) and controls without dementia ( $n = 39$ ), patients were classified with 89% accuracy ( $P < 0.001$ ). Furthermore, in 47 patients with mild cognitive impairment, progression to AD was predicted with 81% accuracy ( $P < 0.001$ ) up to 6 years before clinical diagnosis. Functional profiling of the 18 predictor proteins pointed to involvement in systemic dysregulation of intracellular pathways of immune response, hematopoiesis and apoptosis.

Further tests are needed before this approach can be used in patients, but the identification of blood plasma biomarkers early in the course of AD could open the door to more-effective interventions.

**Original article** Ray S *et al.* (2007) Classification and prediction of clinical Alzheimer's diagnosis based on plasma signaling proteins. *Nat Med* 13: 1359–1362

## Early exposure to mercury-containing vaccines has no consistent effect on neuropsychology

Concerns have been expressed about the potentially negative neuropsychological effects of the mercury-containing preservative thiomersal (thimerosal) in pediatric vaccines; however, a recent cohort study found no evidence to indicate a causal relationship between deficits in neuropsychological functioning at 7–10 years and early exposure to thiomersal-containing vaccines.

The study used standardized tests to assess 42 neuropsychological outcomes in 1,047 children aged 7–10 years; autism-spectrum disorders were not assessed. Each child's exposure to mercury from thiomersal was determined from computerized immunization records, medical records, parent immunization records and parent interviews. The median cumulative exposure to mercury from thiomersal from birth to 7 months was  $112.5 \mu\text{g}$  (range 0– $187.5 \mu\text{g}$ ); 16 children had no thiomersal exposure during this period. After adjustment for potential confounding factors, few significant associations were found between test performance and exposure to thiomersal. Those associations that were detected were small, almost equally divided

between positive and negative effects, and mostly sex-specific. The degree of mercury exposure from birth to 7 months correlated positively with better performance on one test of fine motor coordination in both boys and girls and in one test of achievement (letter and word identification) in boys. A possible adverse effect of neonatal (birth to 28 days) mercury exposure on language development was noted; however, in boys there was a positive association between neonatal exposure to mercury and performance IQ. The authors suggest that the few significant associations observed might simply be chance findings attributable to the large number of statistical tests performed.

**Original article** Thompson WW *et al.* (2007) Early thimerosal exposure and neuropsychological outcomes at 7 to 10 years. *N Engl J Med* 357: 1281–1292

### 🕒 **Neurosonography—a useful bedside tool for strokologists**

Rapid determination of the site and burden of arterial thrombi is crucial following acute stroke, as the speed of recanalization affects the individual's clinical course. Neurosonographic examinations are noninvasive, convenient to use, relatively inexpensive and can be performed at the bedside. The multicenter, observational Eligible Study has now shown that neurosonography can identify the site of clot as early as 3 h after symptom onset and monitor in real time the highly dynamic recanalization process of occluded vessels during treatment for stroke.

A total of 89 consecutive patients with stroke underwent ultrasound assessment (echo color Doppler ultrasound and transcranial color-coded duplex sonography) within 3 h of stroke onset, at 3–6 h and 24–36 h after admission, at day 5, and after 3 months. On the basis of admission ultrasound findings, patients were stratified according to vascular lesion subtype (tandem or T occlusions, middle cerebral artery stenoses or occlusions, and internal carotid artery occlusions or stenosis). The site of clot and degree of stenosis correlated highly with baseline NIH Stroke Scale score ( $P < 0.0001$ ); scores were highest in the patients with T or tandem occlusions (i.e. those with the greatest atherosclerotic burden). Furthermore, modified Rankin Scale score, median NIH Stroke Scale

score and mortality were all significantly different between the groups at 3 months, even after adjustment for treatment. In line with previous findings, the T or tandem occlusion group had the lowest recanalization rates at 3 months and the highest mortality (50%), compared with the highest recanalization rates and no mortality in the patients with middle cerebral artery stenosis or occlusion.

These findings indicate that neurosonography could be a useful bedside tool to assess the neurovascular status in acute stroke and during treatment follow-up.

**Original article** Malferrari G *et al.* (2007) The Eligible Study: ultrasound assessment in acute ischemic stroke within 3 hours. *Cerebrovasc Dis* 24: 469–476

### **Altered epigenetic mechanisms related to GABA synthesis identified in schizophrenic brains**

Abnormalities in the GABA neurotransmitter system are thought to have a role in the development of schizophrenia. Having investigated the molecular mechanisms that underlie these abnormalities, researchers now describe specific alterations in chromatin markers relating to the regulation of genes coding for GAD1 and other key enzymes involved in GABA synthesis.

Trimethylation and monomethylation of histone H3-lysine 4 (processes involved in chromatin remodeling and transcription initiation) increased progressively with age in the human and the mouse cerebral cortex at the *GAD1/Gad1* promoter, as well as at the promoters of other GABAergic gene loci. By comparison, brains from patients with schizophrenia and especially females, showed reduced *GAD1* mRNA expression and H3K4 trimethylation. The study also suggested a role for mixed-lineage leukemia 1 (MLL1), a histone methyltransferase expressed in GABAergic and other cortical neurons, because histone methylation was decreased in MLL1 mice. Finally, the antipsychotic drug clozapine increased *Gad1* H3K4 (tri)methylation in mice, as well as increasing MLL1 mRNA, suggesting that medications aimed at correcting the described mechanistic flaws could be developed.

This research indicates major differences between normal development and schizophrenia. In the normal brain there is progressive increase in H3K4 methylation at GABAergic