are difficulties, further studies targeting inflammation-associated patients with such new tools and approaches should deepen our understanding of the pathophysiology of the disease and lead to the development of new treatments.

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Anatomical brain abnormalities and early detection of autism

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Over the past two decades, a variety of studies have proposed that specific abnormalities in early brain anatomy might be associated with the development of autism spectrum disorder. For example, these reports have included suggestions that an abnormally large brain volume, evident in early head-circumference measures, might be an early biomarker of autism.[1–3] Various follow-up studies, however, have not been able to reproduce these findings,[4–7] thereby questioning the applicability of early head-circumference measures as a biomarker of autism in the general population.

When considering the clinical utility of such biomarkers for autism, two points should be considered. First, given the large heterogeneity of symptoms across individuals with autism and the heterogeneity of hypothesised underlying mechanisms,[8] a single biomarker is highly unlikely to be present in all individuals. Instead, specific biomarkers might be useful for stratifying the heterogeneous autism population into more homogeneous subgroups that could benefit from distinct diagnostic techniques and treatments. Second, most studies regarding autism biomarkers report statistical differences across autism and control groups. The existence of significant between-group differences does not mean that the biomarker exists only in the autism group and not in the control group; instead, such statistical differences mean that the biomarker is more probable in the autism group. A slight difference in probability can achieve statistical significance, but will not necessarily offer clinical utility. To determine clinical utility, the biomarker must be shown to enable accurate identification of many individuals with autism (ie, high sensitivity) while excluding most individuals without autism (ie, high specificity). Most importantly, the specific measure or threshold used must be validated in independent cohorts and must be reliable and generalisable.

In *The Lancet Psychiatry*, Mark Shen and colleagues[9] present results from an impressive, relatively large, well characterised cohort of toddlers (aged 2–3·5 years) with autism spectrum disorder (n=159)

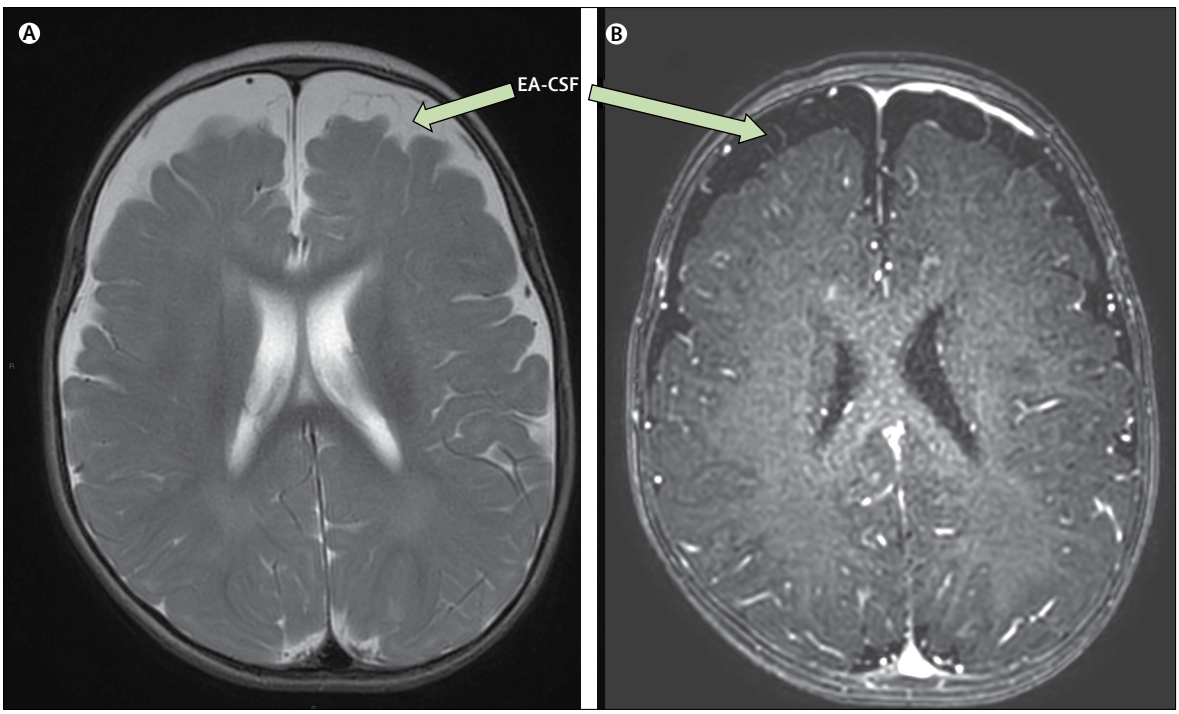

Figure: **Example of benign external hydrocephalus in a 10-month-old infant**
Note the large expansion of EA-CSF volume above the frontal lobes in both the T2-weighted (A) and T1-weighted (B) scans. EA-CSF=extra-axial cerebrospinal fluid.

who were compared with age-matched controls (n=77). The authors analysed anatomical MRI scans of the toddlers using automated image-processing algorithms that quantified the volume of extra-axial cerebrospinal fluid (CSF) in each toddler. They found that toddlers with autism had, on average, 15% more extra-axial CSF than controls. Furthermore, they reported that when selecting an extra-axial CSF threshold of 102 mL, they could accurately identify 133 of the 159 toddlers with autism (84% sensitivity) and accurately exclude 46 of the 77 control toddlers (60% specificity). These findings correspond well with previous reports from the same group, in which similar differences were found in high-risk siblings of children with autism who developed autism, compared with high-risk siblings who did not.[10] Hence, these findings have been reproduced with an independent sample of children, demonstrating the robustness of this measure.

Increases in extra-axial CSF volume in the range described by Shen and colleagues (approximately 15%) fall into the clinical categorisation of benign external hydrocephalus. This type of hydrocephalus is defined as macrocephaly associated with an increase in extra-axial CSF volume, especially above the frontal lobes, without an increase in ventricle volume (figure). Several potential mechanisms for benign external hydrocephalus have been proposed. For example, delayed maturation of arachnoid granulations has been suggested to lead to an imbalance between the production and absorption of CSF, leading to CSF accumulation, mainly in the frontal subarachnoid spaces.[11] Although benign external hydrocephalus has been reported to be associated with later developmental abnormalities, especially in motor function, this condition is considered self-limiting, benign in most cases, and thus rarely treated.[12] Currently, benign external hydrocephalus is not defined by a specific cutoff value of extra-axial CSF volume, and quantitative data regarding the distribution of extra-axial CSF volumes in the typically developing population are scarce.[11]

The reported findings regarding increased extra-axial CSF in at least some children with autism suggest that benign external hydrocephalus might not be entirely benign and might indicate a specific relationship between abnormal CSF circulation and the development of a subgroup of individuals with autism. Epidemiological studies examining the long-term development of infants with benign

external hydrocephalus are, therefore, highly warranted. In addition, accurate quantification of extra-axial CSF volume in infants is necessary for characterising normal extra-axial CSF distributions and defining volumetric boundaries for clinical concern. Additional MRI measures indicative of increased intracranial pressure and CSF composition might augment the potential clinical utility of the extra-axial CSF measure in identifying individuals with poor developmental outcomes. Such studies would enable researchers to assess the validity and clinical utility of the new and exciting autism biomarker proposed by Shen and colleagues.

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Self-harm in older adults: room to improve clinical care

Self-harm and suicide among older adults is a worldwide population health issue.[1] Risk factors for self-harm among older adults have been widely explored, including the influence of mental health conditions, physical illness, and psychosocial factors.[1,2] Self-harm research in older adults has largely focused on describing the incidence and identifying risk factors for self-harm with the use of emergency department presentation, hospital admission, registry, and mortality data. Research examining self-harm among older adults using primary care records is scarce.[3]

In *The Lancet Psychiatry*, Catharine Morgan and colleagues[4] assessed 4124 people aged 65 years or older who had a self-harm episode reported between 2001 and 2014 from the Clinical Practice Research Datalink of 674 registered general practices in the UK. Electronic primary care records enabled follow-up of clinical management, including referrals to mental health specialist services and medications prescribed with linkage to death registrations for mortality data. The authors found at the 12-month follow-up that only 11·7% of older adults who had self-harmed had been referred to a mental health specialist and that, compared with the least socioeconomically deprived areas, adults in the most deprived areas were 33% less likely to be referred for specialist care (hazard ratio [HR] 0·67 [95% CI 0·45–0·99]). 11·8% of adults were prescribed tricyclic antidepressants (TCAs), despite known associations with risk of toxicity in overdose.[5]

Compared with a matched comparison cohort, older adults who had self-harmed had twice the prevalence of a previous mental illness (ratio 2·10 [95% CI 2·03–2·17]) and a 20% higher prevalence of a physical illness (1·20 [1·17–1·23]). The self-harm cohort were up to 20 times more likely to have an unnatural death in the 12 months after the self-harm attempt (HR 19·65 [95% CI 11·69–33·05]) and this risk remained high in later years (3·41 [2·17–5·35]) compared with the comparison cohort.

Through this research, Morgan and colleagues[4] have provided evidence that the clinical management of older adults who self-harm needs to improve,


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