PRESS RELEASE

ESOC 2021 Daily Highlights: Thursday, 2 September

On Day 2 of ESOC 2021, we saw how large and high-quality datasets have been invaluable to stroke researchers who went on to reveal interesting trends and associations in various conditions affecting the blood vessels of the brain.

Genetic studies using big datasets from the UK Biobank and the MEGASTROKE cohort offered novel insights into the genetic substrates for cerebral small vessel disease, intracranial aneurysm and stroke caused by atrial fibrillation. Studies used existing datasets to identify predictors for cognitive decline, helping to advance preventative strategies for dementia.

A topical study on cerebral venous sinus thrombosis following vaccination against COVID-19 was also presented today.

The role of the HTRA1 protease in white matter hyperintensities revealed from genetic data of the UK biobank

White matter hyperintensities (WMHs) are one of the most common manifestations of cerebral small vessel disease, contributing to a significant burden of stroke and dementia. Some rare genetic mutations are responsible for the development of the familial types of WMHs, such as the mutation of the HTRA1 gene. However, little is known about the contribution of rare genetic variants in WMHs burden in the general population.

To explore the association of rare variants and WMHs in the general population, Dr Malik and colleagues analysed MRI imaging and genetic sequencing data of 16,511 individuals from the UK Biobank. The UK Biobank is a large-scale biomedical database containing genetic and health information from approximately half a million UK participants aged 40-69 recruited between 2006 and 2010.

Using a series of genetic tests, the authors identified certain variants in the HTRA1 gene that were significantly associated with increasing volume of WMHs. The frequency of such variants in the UK biobank population was not negligible, being 1 in 450. To put this in context, carriers of a protease domain variant in the HTRA1 gene would have WMHs volumes that were comparable to non-carriers who were about 11 years older.

Does carrying a variant in the HTRA1 protease domain predict WMHs volume better than the well-known risk factors and common genetic variants? The answer is yes, and the authors demonstrated that the presence of such genetic variants alone corresponded to a larger effect than that of common risk factors such as hypertension, diabetes, smoking or being in the upper 99.8 percentile of a polygenic risk score based on common genetic variants.

The authors concluded that their findings highlighted the relevance of the HTRA1 gene, especially the protease domain, for cerebral small vessel disease and other brain injury of presumed vascular origin in the general population beyond rare hereditary arteriopathies. Further studies in other large datasets are needed to better understand the associations of rare variants in the HTRA1 gene and progression of WMHs and other manifestations of cerebral small vessel disease such as lacunes or acute subcortical infarct.

Predicting rupture risk of intracranial aneurysm using genetic risk, aneurysm location, multiplicity, and age at rupture

An intracranial aneurysm (IA) is an abnormal bulge of a blood vessel within the brain. This bulge could weaken the blood vessel wall, making it prone to rupture, resulting in a haemorrhage within the brain.

To predict which IA will rupture and when the risk for rupture is increased is a challenging task. The study conducted by Bakker and colleagues combined genetics risk score (GRS) and clinical risk factors in a meta-GRS model to investigate whether this combined model could improve the prediction of IA rupture.

The genetic association data were obtained from large genome-wide association studies, the model was trained to predict IA rupture on UK Biobank data (1161 IA cases and 407,392 controls) and subsequently validated on data from the Nordic HUNT study (828 IA cases, of which 318 aneurysmal subarachnoid haemorrhage cases, and 68,568 controls).

The study found that meta-GRS model had modest added value to the model of clinical risk factors, and the prediction was better in women. It found that younger age of aneurysm rupture was associated with a higher genetic risk.

Aneurysm growth on brain imaging and the absolute risk of rupture in intracranial aneurysms

Only selected large unruptured intracranial aneurysms (IAs) undergo preventative treatment. The remaining unruptured IAs are monitored for growth on brain imaging, a risk factor associated with increased risk of rupture. The absolute risk of rupture when an aneurysm has grown remained unknown. In an observational study, van der Kamp and colleagues looked at 5166 patients with a total of 6928 unruptured IAs and their follow-up imaging. Of these, 312 patients with 329 aneurysms showed evidence of aneurysm growth on imaging. The absolute risk of rupture of these aneurysms with growth was 2.9% at six months, 4.3% at one year, and 6% at two years. Aneurysm size of 7mm and above was associated with a 4-fold increase in the risk of rupture. Other factors associated with increased risk of rupture were an irregular shape and site of aneurysm. Overall, the risk of rupture in one year ranged from 2 to 10%.

Van der Kamp, the study author, added, "When there is evidence of IA growth on imaging, clinicians need to decide whether to offer treatment. The Tripe S (Size, shape and site) prediction model derived from this study may be useful to estimate rupture risk which can in turn guide treatment discussions with patients."

This study has been published in JAMA Neurology on 30th August, 2021/8/31 https://jamanetwork.com/journals/jamaneurology/article-abstract/2783663

Genetic risk factors in cardioembolic stroke: MEGASTROKE cohort

Cardioembolic stroke, a stroke that is caused by a blood clot from the heart, constitutes more than a quarter of all ischaemic stroke and is associated with high mortality and morbidity. Yet, the genetic architecture of cardioembolic stroke is poorly understood.

Using 362,661 cases with cardioembolic stroke and stroke-free controls from the MEGASTROKE cohort, and also data from a cohort of 1,030,836 individuals with atrial fibrillation (AF), Jara Cárcel-Márquez and colleagues from Spain performed a new technique, multitrait analysis of genome-wide association summary statistics (MTAG), to identify novel loci associated with cardioembolic stroke.

Using the MTAG approach, the study identified 40 novel and significant loci associated with cardioembolic stroke. All but four were known to be associated with AF. Not all AF risk loci were associated with cardioembolic stroke, though, offering some fascinating mechanistic insight. The authors identified that 51 AF risk loci were not associated with cardioembolic stroke in this study. These 51 AF risk loci were

mainly related to cardiac development. In contrast, AF risk loci associated with cardioembolic stroke were associated with muscle contraction and conduction of electrical impulses.

More research is needed to see if a streamlined polygenic risk score including only AF risk loci that were associated with cardioembolic stroke would help better patient risk stratification from the stroke prevention point of view. Furthermore, this very elegantly done study also highlighted multiple candidate genes that can be potentially used for future studies.

Statins did not increase the risk of intracranial bleeding in patients with ischaemic stroke and cerebral microbleeds

Statins are commonly prescribed for secondary prevention after ischaemic stroke. However, some data suggested that they might increase the risk of bleeding in the brain, raising concerns about their routine use in patients with cerebral microbleeds, who are already at higher risk of intracranial bleeding. Dr Prats-Sánchez and colleagues used observational data from the Microbleeds International Collaborative Network (MICON), led by Professor David Werring, to further examine this topic.

MICON included individual-patient level data from 38 population-based and hospital-based prospective cohort studies from 18 countries. Of the 16,632 patients included, 10,812 (65%) patients were started on statins at baseline, and 4,743 (28.5%) had at least one microbleed on brain imaging. At a median follow-up of 1 year, the study found no evidence that statins increased the risk of intracranial bleeding even in those with the highest risk, namely those with microbleeds burden over 20 or in those with strictly lobar microbleeds. Despite being observational, this large study offered clinicians some reassurance when prescribing statins for secondary prevention of stroke in patients with cerebral microbleeds or in those when detection of cerebral microbleeds was not feasible.

Clinicians should consider long-term cognitive sequelae of stroke to strengthen joint prevention strategies for stroke and dementia: Long-term follow up data from the PROGRESS trial

PROGRESS, a randomised controlled trial (Perindopril Protection Against Recurrent Stroke Study), included a total of 6,105 patients with a history of stroke or TIA. The present analysis investigated the effect of randomised, active blood pressure-lowering (perindopril 4 mg daily with/without additional administration of indapamide 2-2.5 mg daily vs placebo) and major predictors of cognitive decline and dementia.

Active blood pressure-lowering treatment was associated with lower odds of cognitive decline and dementia. This is the case for both men and women. Higher education and baseline cognitive function were associated with lower odds for cognitive decline and dementia. Higher diastolic blood pressure and peripheral arterial disease were associated with higher odds for cognitive decline and dementia. For dementia alone, impaired renal function was found to be associated with an increased risk.

Certain sex differences were found: women were less likely to develop cognitive impairment/ dementia than men. Poorer kidney function was more strongly associated with cognitive impairment/ dementia in women than men. Diabetes was more strongly associated in men than women.

“These findings might help guide patient selection in future trials with longer follow-ups. This study might help inform clinicians their strategies for preventing stroke and dementia”, Jessica Gong, the study author, concluded.

Association between oral anticoagulants and the risk of dementia

Non-valvular atrial fibrillation (NVAF) is associated with an increased risk of dementia. Rahman and colleagues wanted to see if treatment with oral anticoagulants (OAC) could mitigate this association and decrease the risk of dementia in patients with NVAF.

A cohort of 142,227 patients with NVAF were identified using the Clinical Practice Research Datalink, a UK primary care medical records database for over 15 million patients from more than 700 general practices. Patients were followed up and had to be exposed to OAC for at least six months.

8,023 new cases of dementia were identified over a mean follow-up of 4.7 years (incidence rate 12.1 per 1000 person-years). The study found that OAC use decreased the risk of dementia (HR: 0.88; 95% CI: 0.84-0.92) compared to non-use. This decrease was evident after 1-2 years of OAC use.

The additional protective effect on the risk of dementia strengthens the need to use OACs in patients with NVAF and should be considered in treatment decisions.

Study sheds light on the treatment of rare cases of blood clotting in the brain following Covid-19 vaccination

This press release was supplied by the investigators and also featured in The Lancet.

A new UCLH and UCL-led observational study of patients with cerebral venous sinus thrombosis (CSVT) following COVID-19 vaccination provides a clearer guide to clinicians trying to diagnose and treat patients by giving more information about the characteristics of this condition when it is caused by the novel condition vaccine-induced immune thrombotic thrombocytopenia (VITT).

VITT is a condition characterised by a blockage of the veins and a marked reduction of platelets, blood components which are an important part of the blood clotting system.

The commonest and severest manifestation of VITT is CVST, in which veins draining blood from the brain become blocked. The new study in The Lancet provides the most detailed observational study of such cases so far, in which 70 patients with VITT-associated CVST following vaccination are compared to 25 with CVST without evidence of VITT.

The authors suggest that some treatments, such as intravenous immunoglobulin, seem to be associated with better outcomes but caution against reading too much into the findings of the observational study, saying that reliable evidence about treatments can only be obtained in a randomised clinical trial.

The NHS's success with the vaccination programme makes the UK a very good place to study rare side-effects of COVID-19 vaccination. The authors started collecting their cases within a few weeks of the discovery of this new condition. They submitted their report within two months of it being reported in the medical literature.

VITT-associated CVST has a very high mortality rate. Even without VITT, CVST is a severe medical condition, with around 4% of patients dying during their hospital admission. In patients with VITT-associated CVST observed in this study, though, the mortality rate during admission was around seven times higher than that, at 29%.

This poorer outcome is explained at least in part because the abnormal blockage of veins is much more extensive in this condition, with more veins blocked both in the head and elsewhere in the body.

Lead author and NHNN consultant neurologist Dr Richard Perry said: “With an illness of such severity, often in young patients who were previously fit and well, doctors have been desperate for evidence regarding treatments that might prevent some of the death and disability that arises from this condition.

“While an observational study is not the ideal platform to provide evidence for which medications work, it may be a long time before we have evidence from randomised clinical trials, the gold standard for testing new treatments. For the moment, we are dependent on observational studies like CAIAC for our evidence.”

The study provides support for the three principles of treatment established so far by the Expert Haematology Panel, based on early work at UCLH and two other European sites:

1. The use of non-heparin-based anticoagulation
2. Give treatments to try to reduce the level of the abnormal antibody that is implicated in this condition, and
3. Avoid trying to bring the platelet count back up to normal levels by giving platelet transfusions.

Christine Roffe, Professor of Stroke Medicine at Keele University, said, “Although there are sound theoretical reasons supporting the adoption of these treatment strategies until now, there has been no clinical evidence for their use. In our study, non-heparin blood thinners and intravenous immunoglobulin were both associated with better patient outcomes, providing the first clinical evidence from a large case series in support of these treatments.”

Alastair Webb, a consultant neurologist at the John Radcliffe Hospital in Oxford, said: “We found that those patients who were given intravenous immunoglobulin – the treatment in which the body is flooded with normal antibodies to try to reduce the effects of the abnormal one – were more likely to leave the hospital alive and able to live an independent life rather than depending on carers or family to look after them.

“Use of non-heparin blood thinners was similarly associated with a more favourable outcome. Our data do not prove that these treatments work, as the most severely affected patients may have been too unwell to receive them in time, but the results support their use whilst we seek better evidence,” he said.

On the other hand, platelet transfusions were associated with a worse outcome in patients with VITT-associated CVST. Although observational data cannot prove harm from this treatment approach, the study supports the concern that has already been raised about the potential harm of platelet transfusions.

UCLH consultant haematologist Professor Marie Scully said: "Tempting though it might be to replace the platelets that are missing in this condition by infusing new platelets from blood donors, we do not advise this approach. However, it is difficult in cases requiring neurosurgical interventions, and in such situations, they are required to prevent bleeding. Presumably, the reason why the number of platelets in the bloodstream is so low in VITT is that they are quickly used up by abnormal clotting. Infusing more platelets may simply add more fuel to the fire."

Although VITT-associated CVST is a severe condition, it appears to be extremely rare. The authors stress that, for most individuals, the risk to their health of not getting vaccinated against COVID-19 is likely to be much higher.

The paper is available online from the Lancet:
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)01608-1/fulltext

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Notes to Editors:

A reference to the European Stroke Organisation (ESO) Conference must be included in any coverage or articles associated with this study and research.

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About ESO:
The European Stroke Organisation (ESO) is a pan-European society of stroke researchers and physicians, national and regional stroke societies, and lay organisations, founded in December 2007. The ESO is an NGO comprised of individual and organisational members. The aim of the ESO is to reduce the burden of stroke by changing the way that stroke is viewed and treated. This can only be achieved by professional and public education and making institutional changes. ESO serves as the voice of stroke in Europe, harmonising stroke management across the whole of Europe and taking action to reduce the burden.

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7th European Stroke Organisation Conference

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