Research to Understand Stroke due to Haemorrhage

2020 Newsletter

On, despite COVID-19

Although 2020 was one of the most challenging years for us all and the pandemic stopped some of our research studies, there were many positives. Our staff and studies adapted to the pandemic, whilst some staff joined responses to COVID-19.

Research nurse team

Our studies, and many others, are support by a team of research nurses in Edinburgh, led by Allan Macraild. Senior research nurses Seona Burgess, Michelle Coakley and Jessica Teasdale work closely with Allan to support these studies, which are often an important part of our patients' experience. COVID-19 research became a priority for the team for a large part of the year (Allan is illustrated in PPE in the image above). The challenges faced were immense. The team were proud to recruit to COVID-19 studies, including the Oxford vaccine and RECOVERY trials.

Chris Lerpiniere (pictured), our research nurse manager, worked with the Bereavement Service. In April,

Chris was seconded to the ICECAP research team, whose aim was to have a better understanding of COVID-19, by examining tissue taken at post-mortem from patients who had died of COVID-19. They established a tissue bank to help COVID research both nationally and internationally.

Stroke research studies were put on hold for some of 2020, but the research nurses managed to re-open stroke studies despite the pandemic and dealing with their domestic lives, which included house building and marriage!

Leading in a pandemic

RUSH is led by Rustam Al-Shahi Salman, who's a consultant neurologist and professor of clinical neurology in Edinburgh.

In 2020, as a doctor he had to adapt his clinical practice to care for patients with stroke during the pandemic. As a researcher, he had to pause or adapt his studies to the pandemic. Although he knew that taking on three additional leadership positions in 2020 would be challenging, the pandemic made them harder!

As the new president of the British Association of Stroke Physicians, Rustam led the professional Association through the pandemic, surveyed clinical practice, campaigned for patients' care and better PPE for staff, wrote a new strategy for the Association, and set up a new regular meeting to support all national stroke clinical leads and charities in the UK and Ireland.

Rustam became clinical director of the Edinburgh Clinical Trials Unit (ECTU), which conducts randomised clinical trials, which are the most reliable tests of treatment, as we have seen with COVID-19. Following an external review of ECTU, he consulted widely and wrote a strategy to develop, design and

deliver Edinburgh's growing portfolio of clinical trials.

Finally, Rustam became the head of the cerebrovascular research group at the University of Edinburgh, which involves a diverse group of more than 20 principal investigators, and many other researchers.

All of these roles involved keeping people connected, communicating, and supported during the pandemic.

Nonetheless, Rustam escaped at times to help with home schooling and celebrating his 50th birthday on his road bike (pictured above, beside the Crinan Canal).

New personal assistant

Leadership is impossible without support from a team, and Rustam was fortunate that Elaine Lord joined him in August 2020 as PA and administrator of the Cerebrovascular Research Group. Elaine has worked at the university for 20 years and is slowly getting to grips with the complexities of Rustam's diary (always full!) and all of the RUSH projects. Away from work, Elaine is a keen hobby crafter & DIY enthusiast.

Cavernomas: why CARE?

After more than 20 years of studying the patients in the Scottish Audit of Intracranial Vascular Malformations, and identifying in 2015 that the top uncertainty for patients with cavernoma is, "Does treatment (with neurosurgery or stereotactic radiosurgery) or no treatment

improve outcome for people diagnosed with brain or spine cavernoma?", the National Institute of Health Research (NIHR) commissioned research to answer this question in 2018.

Rustam was fortunate to lead a successful collaborative application to the NIHR for the, "Cavernomas A Randomised Effectiveness (CARE) pilot trial", to address the effectiveness of treatment including surgery versus treatment without surgery in people with symptomatic brain cavernoma. This NIHR Health Technology Assessment trial grant (£973,835) was awarded in 2020. More details are available: https://fundingawards.nihr.ac.uk/award/NIHR128694. The CARE pilot trial will start in 2021…

Lowering blood pressure after brain haemorrhage

Our BHF clinical research training fellow, Tom Moullaali and his one-year-old son, Rory,

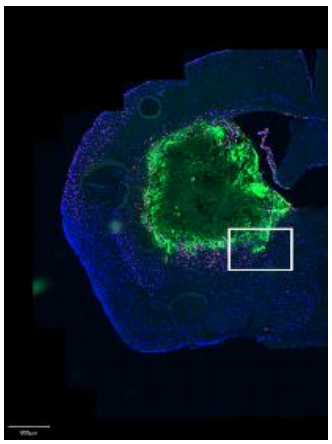
had the unexpected benefit of many more hours together during the COVID-19 lockdown. In 2020, Tom led a team effort that improved the proportion of people with brain haemorrhage who were discharged from hospital with appropriate blood pressure-lowering medication in NHS Lothian **from 62% to 76%**. This involved educating healthcare professionals and patients about the importance of good blood pressure control. It also involved offering patients an opportunity to participate in blood pressure monitoring activities that aimed to help them achieve better blood pressure control.

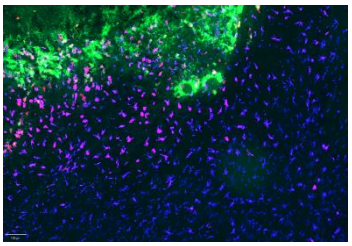
Tom finishes his PhD in January 2021. Tom has secured a position to complete his training to be a neurologist in Edinburgh, which means he can continue to contribute to RUSH. Hooray!

Brain donation

Jack Barrington is a postdoctoral research fellow working to uncover complex actions of the immune system following stroke due to haemorrhage. Jack is performing cutting-edge scientific techniques on donated patient samples to examine white blood cells in microscopic detail. We think white blood cells have a really important role following bleeding in the brain. Our hope is that Jack's research will identify ways to promote beneficial actions and limit harmful ones.

Caoimhe Kirby is heading into the final year of her lab-based PhD. She has been studying the immune cells that accumulate in the brain after a haemorrhage. Studying these cells in brain tissue donated by patients who died from a brain haemorrhage has greatly improved our understanding of these immune cells. Caoimhe is also using a mouse model of brain haemorrhage to test a new drug that boosts these immune cells in the hope of improving outcome after a bleed in the brain. This scan of a mouse brain shows in green the extent of a brain haemorrhage. This is similar to what happens when patients have a stroke due to bleeding. The white box indicates the area that we have zoomed in on in the image below. In blue we can see the immune cells of the brain.





Those that stain pink are immune cells that are responding to the bleed. These responses might be helpful or harmful, or both. We hope to

understand what these cells are doing and whether we can alter their responses.

Jack's and Caoimhe's research could lead to the design of new treatments for stroke due to haemorrhage. This could not happen without brain tissue. We are, extremely thankful to everyone who has contributed to our tissue banks and joined our mission to find new treatments.

Swelling after brain haemorrhage

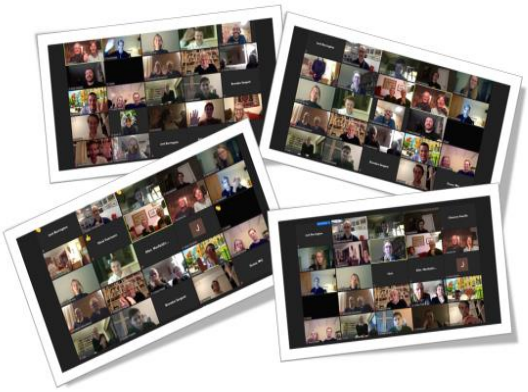
Dr Jamie Loan is a neurosurgery trainee who is working on a PhD with the RUSH group. He took three months out from his PhD to work in the Emergency Department during the first wave of the COVID-19 pandemic. He had led a team to measure swelling shown by the brain scans of hundreds of patients with brain haemorrhage in Lothian. They found that the amount of swelling on a patient's first brain scan does seem to affect outcome, and the paper will soon be published in the *International Journal of Stroke*.

Dr Nesh Samarasekera, is leading the NICHE project to understand how swelling changes over time after brain haemorrhage. Changes in swelling over time are likely to affect outcome, even though swelling on the first scan may not. Despite being unable to recruit patients during the first wave of the pandemic, the research nurses have done really well to get recruitment to NICHE back on target. Well done!

In 2020, Nesh also won a British Heart Foundation Centre for Research Excellence pump priming award of £46,741 to conduct an individual patient data meta-analysis of the

association between peri-haematomal oedema and outcome after spontaneous intracerebral haemorrhage.

Arthur Fonville Awards for Stroke Research



Like everything in 2020 the sixth annual award ceremony was a virtual event.

Again, there was a very strong field of applicants. Following independent scoring by multiple reviewers, the awards went to: Maritta van Stigt (PhD candidate at Academisch Medisch Centrum, University of Amsterdam) for her dissertation, “Identification of large vessel occlusions in patients with suspected stroke using ambulant electroencephalography”, and Brendan Sargent (medical student at the University of Edinburgh) for his dissertation, “A cohort study of the effects of perihaematomal oedema on long-term outcomes of intracerebral haemorrhage.”

The extended Fonville family and many friends attended the ceremony virtually from The Netherlands. Joost & Catherine presented the award of £100 (as well as the Arthur Fonville Stone, pictured below) with the opportunity of a further £750 towards presenting the projects at a national stroke conference, either in person or virtually.

Patient Reference Group

Our patient reference group have been invaluable again this year.

They advise us about the design of our research. They contribute to grant applications. They oversee the progress of our research. They sit on the committees that supervise our research. They occasionally attend research ethics meetings. They often give us great ideas.

You can find out more via our website www.RUSH.ed.ac.uk:

If this is something you might like to help with, please contact Rosemary (details below).

Raising money for RUSH

If you would like to fundraise for us, please contact Kerry MacKay (0131 650 9221).

Contact us:

We are always happy to hear from the participants in our studies, or their relatives or carers.

Feel free to contact us using any of the methods described below:

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Donations to our research programme:
Single donation http://edin.ac/1iNmqj0,
regular donation http://edin.ac/1iNmwqV

Publications in 2020 that involved the RUSH team:

1. Cheng X, Su Y, Wang Q, Gao F, Ye X, Wang Y, Xia Y, Fu J, Shen Y, Al-Shahi Salman R, Dong Q. Neurofilament light chain predicts risk of recurrence in cerebral amyloid angiopathy-related intracerebral hemorrhage. Aging 2020;12(23):23727-38

2. Almarzouki A, Wilson D, Ambler G, Shakeshaft C, Cohen H, Yousry T, Al-Shahi Salman R, Lip GYH, Houlden H, Brown MM, Muir KW, Jäger HR, Werring DJ. Sensitivity and specificity of blood-fluid levels for oral anticoagulant-associated intracerebral haemorrhage. Sci Rep 2020;10(1):15529

3. Hald SM, Sloth CK, Agger M, Schelde-Olesen MT, Højholt M, Hasle M, Bogetofte H, Olesrud I, Binzer S, Madsen C, Krone W, García Rodríguez LA, Al-Shahi Salman R, Hallas J, Gaist D. The Validity of Intracerebral Hemorrhage Diagnoses in the Danish Patient Registry and the Danish Stroke Registry. Clinical Epidemiology 2020;12:1313-25

4. McLernon S, Schwarz G, Wilson D, Ambler G; Goodwin R, Shakeshaft C, Cohen H, Yousry T, Al-Shahi Salman R, Lip GYH, Houlden H, Brown MM, Muir KW, Jäger HR, Terry L, Werring DJ on behalf of the CROMIS-2 Collaborators. Association between critical care admission and 6-month functional outcome after spontaneous intracerebral haemorrhage. J Neurol Sci 2020;418:117141

5. Best JG, Barbato C, Ambler G, Du H, Banerjee G, Wilson D, Shakeshaft CE, Cohen H, Yousry TA, Al-Shahi Salman R, Lip GYH, Houlden H, Brown MM, Muir KW, Jäger HR, Werring DJ. Association of enlarged perivascular spaces and anticoagulant-related intracranial hemorrhage. Neurology 2020; 95:e2192-e2199

6. Varatharaj A, Thomas N, Ellul MA, Davies NWS, Pollak TA, Tenorio EL, Sultan M, Easton A, Breen G, Zandi MS, Coles JP, Manji H, Al-Shahi Salman R, Menon DK, Nicholson TR, Benjamin LA, Carson A, Smith C, Turner MR, Solomon T, Kneen R, Pett SL, Galea I, Thomas RH, Michael BD, on Behalf of the CoroNerve Studies Group. UK-wide surveillance of neurological and neuropsychiatric complications of COVID-19: The first 153 patients. Lancet Psychiatry 2020;7:875-82

7. Mohr JP, Overbey JR, Hartmann A, von Kummer R, Al-Shahi Salman R, Kim H, van der Worp HB, Parides MK, Stefani MA, Houdart E, Libman R, Pile-Spellman J, Harkness K, Cordonnier C, Moquete E, Biondi A, Klijn CJM, Moskowitz AF. Medical management with interventional therapy versus medical management alone for unruptured brain arteriovenous malformations (ARUBA): final follow-up of a multicentre, non-blinded, randomised controlled trial. The Lancet Neurology 2020;19:573-81

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9. Zhou Z, Malavera A, Yoshimura S, Delcourt C, Mair G, Al-Shahi Salman R, Demchuk AM, Wardlaw JM, Lindley RI, Anderson CS. Clinical prognosis of FLAIR hyperintense arteries in ischaemic stroke patients: a systematic review and meta-analysis. JNNP 2020;91:475-82

10. Ratelade J, Klug N, Lombardi D, Angelim MKSC, Dabertrand F, Domenga-Denier V, Al-Shahi Salman R, Smith C, Gerbeau J-F, Nelson MT, Joutel A. Reducing hypermuscularization of the transitional segment between arterioles and capillaries protects against spontaneous intracerebral haemorrhage. Circulation 2020;141:2078-94

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12. Rannikmae R, Ngoh K, Bush K, Al-Shahi Salman R, Doubal F, Flaig R, Henshall DE, Hutchison A, Nolan J, Osborne S, Samarasekera N, Schnier C, Whiteley WN, Wilkinson T, Wilson K, Woodfield R, Zhang Q, Allen N, Sudlow CLM. Accuracy of identifying incident stroke cases from linked healthcare data in UK Biobank. Neurology 2020;95:e697-e707

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14. Banerjee G, Chan E, Ambler G, Wilson D, Cipolotti L, Shakeshaft C, Cohen H, Yousry T, Al-Shahi Salman R, Lip GYH, Muir KW, Brown MM, Jäger HR, Werring DJ, on behalf of the CROMIS-2 collaborators. Cognitive impairment before atrial fibrillation-related ischemic events: neuroimaging and prognostic associations. J Am Heart Assoc 2020;9:e014537

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