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P 299

Novel mutations associated with cerebral cavernous malformations in an Italian cohort of patients

S. Lanfranconi[1], D. Ronchi[1,2], G. Valcamonica[1,2], L. Valentino[1,2], G. A. Bertani[3], S. P. Corti[1,2], N. Bresolin[1,2], G. P. Comi[1,2]

[1]Neurology, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico di Milano, Milan, Italy
[2]Dino Ferrari Center, University of Milan, Milan, Italy
[3]Neurosurgery, Fondazione IRCCS Cà Granda Ospedale Maggiore di Milano, Milan, Italy

Question: Cerebral cavernous malformations (CCM) are vascular abnormalities of the central nervous system characterized by clusters of enlarged, leaky capillaries. They can occur either sporadically or as a familial autosomal dominant disorder (FCCM) characterized by incomplete clinical and neuroradiological penetrance. The most common presenting features are recurrent headache, focal neurological deficits, cerebral hemorrhage and seizures. This condition is caused by heterozygous mutations altering the reading frame of KRIT1, CCM2, or PDCD10, which are involved in angiogenesis and endothelial permeability. We aimed to perform a molecular screening in an Italian cohort of Italian cohort of patients with cerebral cavernous malformations. **Methods:** Over a four years period 21 patients from 13 families underwent genetic screening at Policlinico Hospital of Milan. Multiple lesions (n >= 2)and/or positive familial history were mandatory to undergo genetic testing. We analyzed all exons and intronic boundaries of KRIT1, CCM2 and PDCD10 by Sanger sequencing. MLPA analysis with commercially available kits was used to detect large-scale rearrangements. RT-PCR analysis using cDNA retrotranscribed from blood leukocytes RNA evaluated the functional effects of the candidate variants. **Results:** A molecular diagnosis was established in 10 independent probands (76.9%) of our cohort. Nine independent mutations were found: four of them are novel. Causative mutations in KRIT1 were detected in 4 familial and 3 sporadic cases. CCM2 mutations accounted for 2 familial and 1 sporadic case. Segregation test was positive in familial cases. No mutation was found in PDCD10. **Conclusion:** Neuroradiological findings followed by full molecular analysis of KRIT1 and CCM2 allowed a firm diagnosis in 76.9% of our cohort of CCM patients. These findings are useful in view of future therapeutic approaches.

P 301

Thrombin upregulation after intracerebral hemorrhage is associated with hematoma expansion and poor neurological outcome

N. Wenger[1], F. Liu[2], M. Yehya[2], X. Zou[2], Y. Zhu[2], M. Torbey[2]

[1]The Ohio State University College of Medicine, Columbus, United States
[2]Neurology, Wexner Medical Center at The Ohio State University, Columbus, United States

Introduction: Intracerebral hemorrhage (ICH) is a type of stroke with no therapy proven by randomized controlled trial. Hematoma expansion after ICH has been associated with worse outcomes and hence is a potential therapeutic target. Thrombin has been shown to cause the brain edema that can arise after ICH, but hematoma expansion is a stronger predictor of ICH outcomes than edema. **Objectives:** We sought to characterize the relationship between post-ICH hematoma expansion and thrombin, thrombin inhibitor protease nexin-1 (PN-1), and neurological deficits in a rat model of ICH. **Materials and methods:** We induced an ICH in adult male rats with injection of collagenase type IV (0.1 U) into left striatum. We performed a modified Neurological Severity Score (NSS), TruScan moving time, Rotarod and cylinder test at 3, 6, 24, 48 and 72 hours after ICH. Rats were sacrificed at 1, 3, 6, 12, 24 and 72 hours after ICH. Western blotting was used to determine thrombin and PN-1 protein levels in the area of injury. The resolution of protein bands was compared between each group. Hematoma volume was assessed histologically. **Results:** After induction of ICH, hematoma volume increased at each time point ($n = 3$, $p < 0.05$) until leveling off at 24 hours, with no significant hematoma expansion after one day had passed ($p > 0.05$). There was a significant increase in both thrombin and PN-1 levels in injured rats compared to controls. The peak increase of PN-1 levels preceded the increase in thrombin levels. PN-1 level increased within 1 hour of injury and peaked at 3 hours, remaining above control levels until 72 hours ($n = 3$, $p < 0.01$ vs control at 1H, 3H, 6H and 24H). Thrombin level started to increase at 6 hours and peaked 24 hours after ICH ($n = 3$, $p < 0.001$ vs control at 6H, 24H and 72H). All measures of neurological deficit were worst at 24 hours post injury. **Conclusion:** Maximum hematoma volume 24 hours after ICH is associated with peak thrombin levels and poor neurological function. Furthermore, the initial increase in PN-1 may have neuroprotective properties as it precedes thrombin release. Manipulating thrombin or PN-1 may affect hematoma expansion and neurological deficit, and these associations warrant further investigation.

P 302

Impact of seizures and status epilepticus on hospital utilization, in-hospital mortality, palliative care, hospital charges and length of stay among intracerebral hemorrhage (ICH) patients

P. Piriyawat, M. R. Afzal, M. A. Qureshi, R. Khatri, G. J. Rodriguez, A. Maud, S. Cruz-Flores

Neurology, Texas Tech University , El Paso, United States

Objective and background: To determine the effect of seizures/status epilepticus in ICH patients on hospital utilization in-hospital complications, procedures, length of stay, hospital charges, in-hospital mortality, palliative care (PC) and do not resuscitate (DNR). **Methods:** We identified our intracerebral hemorrhage (ICH) patient subset from Nationwide Inpatient Sample database for years 2011-2014 using codes (DX1 = 431, 432.0, 432.1, 432.9) from the International Classification of Diseases, 9th edition. ICH patients who developed in-hospital seizures (DX = 345 or 780.3) or status epilepticus (DX = 345.3) were determined by using secondary (Dx2…..Dx25) ICD-9 codes. Baselines variables where compared among ICH patients with and without seizures/status epilepticus with univariate analysis. Exposures of interest included in-hospital seizures and in hospital status epilepticus. Outcomes of interest included in hospital complications and mortality, length of stay, and life-saving and life-sustaining therapies included but not limited to mechanical ventilation, gastrostomy, ventriculostomy, craniotomy. In the multivariate analysis, ICH without seizures/status epilepticus served as the reference group and the OR were adjusted for age, gender, race, and comorbidities. **Results:** Of 3,91778 hospitalized patients with ICH, 341242 (87.1%), 48075 (12.3%), and 2461 (0.6%) were ICH without seizures/status epilepticus, ICH with seizures, and ICH with status epilepticus respectively. In univariate analysis, ICH with either seizures/status epilepticus had higher rate of in-hospital complications (MI, sepsis, pneumonia, DVT, PE and UTI), in-hospital procedures (mechanical ventilation (MV), gastrostomy and transfusions, ventriculostomy, ventriculoperitoneal (VP) shunting, intracranial pressure monitoring, craniectomy and craniotomy), compared to ICH without seizures/status epilepticus. Mean LOS and hospital charges were also higher for ICH with either seizures/status epilepticus. Similarly, ICH with either seizures/status epilepticus had higher rate (P-value = <.05) of in-hospital mortality, palliative care (PC) and do not resuscitate (DNR) compared to ICH without seizures/status epilepticus. In multivariate analysis, ICH with either seizures/status epilepticus had higher rate of in-hospital procedures (MV, gastrostomy, transfusions, and VP shunting), in-hospital mortality, PC and DNR compared to ICH without seizures/status epilepticus. **Conclusion:** ICH patients with seizures in the hospital represent 12% of cases and status epilepticus is uncommon (0.6%). Importantly, in patients with ICH, seizures and status epilepticus significantly increase the rate of in-hospital complications/procedures, length of stay, in-hospital charges, and in-hospital mortality.

P 303

Impact of seizures and status epilepticus on hospital utilization, in-hospital mortality, hospital charges and length of stay among subarachnoid hemorrhage (SAH) patients

P. Piriyawat, M. R. Afzal, A. Maud, M. A. Qureshi, G. J. Rodriguez, D. Kassar, S. Cruz-Flores

Neurology, Texas Tech University , El Paso, United States

Objective and background: To determine the effect of developing in-hospital seizures/status epilepticus in SAH patients on in-hospital complications, procedures, length of stay, hospital charges, in-hospital mortality, palliative care (PC) and do not resuscitate (DNR). **Methods:** We identified our subarachnoid hemorrhage (SAH) patient subset from Nationwide Inpatient Sample database for years 2011-2014 using codes (DX1 = 430) from the International Classification of Diseases, 9th edition. SAH patients who developed in-hospital seizures (DX = 345 or 780.3) or status epilepticus (DX = 345.3) were determined by using secondary (Dx2….. Dx25) ICD-9 codes. Univariate analysis was performed to compare SAH without seizures/status epilepticus with ICH with seizures/status epilepticus baseline variables: age, gender, race, medical comorbidities, in-hospital complications and procedures, length of stay (LOS), total hospital charges, in-hospital mortality, palliative care (PC) and do not resuscitate (DNR). In the multivariate analysis, SAH without seizures/status epilepticus served as the reference group and results were adjusted for age, gender, race and comorbidities. **Results:** Out of 101,576 hospitalized patients with SAH, 89,203 (87.8%), 11,752 (11.5%), and 620 (0.6%) did not have seizures/status epilepticus, were SAH with seizures, and SAH with status epilepticus respectively. In univariate analysis, SAH with either seizures/status epilepticus had higher rate of in-hospital complications (sepsis, pneumonia, DVT, and UTI), in-hospital procedures (mechanical ventilation (MV), gastrostomy and transfusions), compared to SAH without seizures/status epilepticus. Mean LOS and hospital charges were also higher for SAH with either seizures/status epilepticus. Similarly, SAH with either seizures/status epilepticus had higher rate of in-hospital mortality and palliative care (PC) compared to SAH without seizures/status epilepticus. After adjustment in multivariate analysis, SAH with either seizure/status epilepticus had higher rate of in-hospital procedures (MV, and gastrostomy), in-hospital mortality, and PC compared to SAH without seizures/status epilepticus. **Conclusion:** Seizures and status epilepticus affect 11.5% and 0.7% respectively of patients with SAH and they significantly increase the rate of in-hospital complications/procedures, length of stay, in-hospital charges, and in-hospital mortality.

P 304

Cortical vein thrombosis – case presentation

C. Pascu, C. Laza, A. R. Stanca, A. Hancu

Neurology Clinic, Clinical Emergency County Hospital Constanta, Constanta, Romania

Introduction: Cortical venous thrombosis (CVT) without concomitant dural sinus thrombosis is an uncommon disorder. Multiple factors have been associated with CVT, but only some of them are reversible. Prior medical conditions (eg, thrombophilias, inflammatory bowel disease), transient situations (eg, pregnancy, dehydration, infection), selected medications (eg, oral contraceptives, substance abuse), and unpredictable events (eg, head trauma) are some predisposing conditions. **Methods:** We present the case of a 17 years old patient who was examined 6 days after a seizure. He had complained of a mild headache and had no medical history. During the days prior to the seizure, the subject experienced symptoms such as fatigue, frontal headache,sore throat, subfebrility. We performed standard lab tests, an EEG and a cerebral MRI. **Results:** The EEG and lab tests were normal. The MRI showed a thrombotic cruoric process of the right frontoparietal cortical vein in acute stage, adenoid vegetation, and right mastoiditis. He was evaluated for antiphospholipid syndrome and for thrombophilia and anticoagulation was initiated. The tests came positive for lupus anticoagulant and homozygous genotype for the A1298C mutation of MTHFR gene. It is advisable that the tests for lupus anticoagulant be repeated after 12 weeks. **Conclusion:** Isolated cortical vein thrombosis is an uncommon condition and often difficult to diagnose, both clinically as well as radiologically. In this case, multiple risk factors are present: inherited thrombophilia, possible ENT infection.

P 305

Does the unruptured intracranial aneurysm treated score (UIATS) have a high risk of rupture threshold?

P. Piriyawat, M. A. Qureshi, M. R. Afzal, R. Khatri, S. Cruz-Flores, G. J. Rodriguez

Neurology, Texas Tech University , El Paso, United States

Objective: By comparing the UIATS score among patients with ruptured aneurysms with the score among those patients with unruptured aneurysms. Determine if the score a priory would have been substantially different indicating a higher risk in those presenting with subarachnoid hemorrhage (SAH) Background: Unruptured Intracranial Aneurysms (UIA) occur in about 3% of the adult population and are often detected incidentally on imaging. The appropriate approach to manage patients with UIA"s remains disputable given the multiple factors influencing the natural history, risk of rupture in comparison to the risks of interventions **Design/methods:** We report a retrospective single-center study of patients treated at the Texas Tech Hospital , El Paso between 2011 to 2016 . Medical records of 198 patients were reviewed and 87 patients were found to have aneurysms in the Basilar artery bifurcation,

Vertebral/Basilar artery and Anterior & Posterior communicating arteries that fit the UIATS criteria. We then calculated the UIATS score among those with SAH and compared them with those with an unruptured aneurysm. Results: Out of 87 patients, 36 (41.4%) were diagnosed with unruptured aneurysms and 51 (58.6%) with ruptured. 34 patients in the unruptured group underwent invasive procedures and 2 were managed conservatively. The mean age for the unruptured versus ruptured aneurysms (58.89 ± 12.17 versus 57.12 ± 14.02, p-value 0.542). The mean score for the unruptured vs ruptured aneurysms was similar(22.97 ± 4.28 vs 21.23 ± 4.80, p-value 0.086). Interestingly, the mean score of those in the unruptured group was lower among those treated as compared to those in observation (22.83 ± 4.35 vs 27.50 ± 2.12, p-value 0.148). **Conclusions:** Based on these findings, the role of UIATS score in stratifying patients for conservative vs interventional treatment is questionable

P 306

Hydrocephalus after spontaneous subarachnoid haemorrhage

V. Smolanka, **T. Havryliv**, A. Smolanka, F. Pavuk

Neurosurgery, Uzhhorod National University, Uzhhorod, Ukraine

Objective: to determine the influence of hydrocephalus on treatment results among patients with spontaneous subarachnoid haemorrhage (sSAH). **Materials and methods:** two hundred and forty-two consecutive patients with sSAH who were treated between january 2006 and january 2016, at Uzhhorod Regional Clinical Center of Neurosurgery and Neurology, were retrospectively studied. 66% of patients were operated (61% - were treated with "open" techniques (lamina terminalis was not routininely fenestrated), and 5% - underwent endovascular repair). **Results:** overall, 33 of the 242 patients (13,6%) developed acute hydrocephalus after sSAH. The study population consisted of 17 male and 16 female patients and the mean age was 49.6 years (range, 24–66 yr). Intraventricular hemorrhage was present in 15 (45%) patients. Intracerebral hematoma was present in 17 (52%) of cases. The overall mortality in hydrocephalus group was 55%, compared with 14% between all patients with sSAH. **Conclusion:** the presence of hydrocephalus in patients SAH is predictor of poor treatment results. Early and aggressive treatment of this targeted population might help decrease morbidity rates and improve outcomes.

P 307

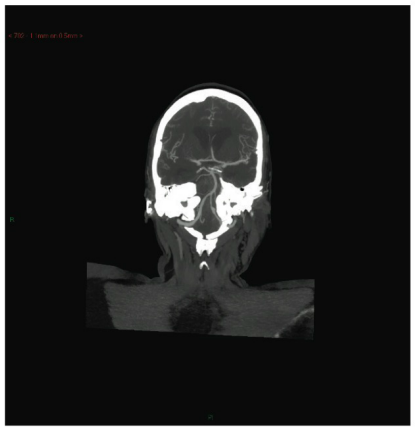
An interesting case of subarachnoid haemorrhage with intracranial vertebral artery (v4) aneurysm dissection - presentation, neuroimaging and management

J. Paton[1], S. Ghosh[1], S. Unnam[2]

[1]Stroke / Care of the Elderly, University Hospital Crosshouse, Kilmarnock, United Kingdom
[2]Radiology, University Hospital Crosshouse, Kilmarnock, United Kingdom

Intracranial vertebral artery dissection is an uncommon but important cause of both subarachnoid haemorrhage and ischaemic stroke. Intracranial arterial dissection is often clinically catastrophic and generally confers a worse outcome than extracranial arterial dissection[1]. This case study details a 43 year old lady who presented with severe headache, left-sided weakness and speech disturbance. Her CT angiogram on admission was reported as showing no vascular abnormality. Three days later she developed further headache, with subsequent generalised seizure and impaired consciousness. Repeat CT showed large volume SAH, with significant hydrocephalus and further CTA revealed a dissecting 4mm V4 aneurysm (with hindsight and neuroradiology expertise, this aneurysm was determined as being visible upon initial CTA at time of presentation, albeit subtle appearance). She was transferred to a Neurosurgical Tertiary Centre and underwent right frontal EVD and subsequent therapeutic permanent occlusion of the left vertebral artery, undertaken by the Neuro-interventional Radiologists. This case represents an unusual aetiology of SAH, the literature surrounding which is somewhat scarce. It is thought that patients presenting with such usually have poor outcomes, however this lady in fact made full recovery, returning to our District General Hospital for a short period of rehabilitation, before ultimately being discharged home. [1] Li, Simon, Yan et al – Prognosis of intracranial dissection relates to site and presenting features. *Journal of Clinical Neuroscience 2011-06-01, Volume 18, Issue 6, Pages 789-793.*

Figure 1



P 308

Extensive cerebral venous thrombosis in a young woman

C. Laza[1], A. G. Bardas[2], V. Taran[3], A. Hancu[1]

[1]Neurology, Emergency County Clinical Hospital, Constanta, Romania
[2]Radiology, Emergency County Clinical Hospital, Constanta, Romania
[3]Medimar Imagistic Services, Constanta, Romania

Question: Thrombosis of the cerebral veins is a less common cause of stroke than arterial disease but is an important nosological entity because of the important possible sequelae and long-term implications. **Method:** We present the case of a 39 year-old female smoker, with no known comorbidities, hospitalised for intense occipital headache that had started one day before presentation and who suffered an episode of loss of consciousness, without involuntary movements or sphincter relaxation, in the morning of hospital admission. The history was positive for long-term use of oral contraceptives. The clinical examination on admission was unremarkable, except for a positive Babinski sign on the right side. **Results:** The blood tests revealed mild inflammatory syndrome with no specific cause and infirmed possible pregnancy. The EEG did not show any pathologic changes. The cerebral CT scan raised the question of a right transverse cerebral sinus thrombosis. The MRI scan showed extensive thrombosis of the right side cerebral venous system, affecting the transverse and sigmoid sinuses and the internal jugular vein. The patient was started on low molecular weight heparin and subsequently switched on anti-vitamin K oral anticoagulants. The screening for hypercoagulable states was unremarkable. The clinical progress was favorable and the patient was released from the hospital after 10 days. She is to continue vitamin K antagonist treatment for at least 3 months and to stop smoking and using oral contraceptives. **Conclusion:** Smoking and oral contraceptive use are known risk factors for cerebral venous thrombosis. We chose to present this case because of the discrepancy between the clinical and imagistic findings.

P 309

The changes in clot microstructure in patients with haemorrhagic stroke are similar to those with ischaemic stroke – a prospective observational study

A. Sabra[1], S. Stanford[1], M. Lawrence[1], S. Storton[2], V. Evans[1], K. Hawkins[1], M. Wani[2], P. R. Williams[1], P. Evans[1]

[1]Swansea University, Swansea, United Kingdom
[2]Stroke Medicine, Morriston Hospital, Swansea, United Kingdom

Background: We have previously reported a new haemorheological technique measuring clot microstructure (Fractal Dimension (*df*)) ex-vivo and real-time clot formation time (T_{GP}) in patients with ischaemic stroke. These biomarkers confirmed a hypercoagulability state in ischaemic stroke due to the development of an abnormally dense clot structure, as compared to healthy subjects. We aimed to evaluate these novel clotting biomarkers in haemorrhagic stroke (HS). **Methods:** In a prospective cohort study, fractal Dimension (*df*) and real-time clot formation time (T_{GP}) were measured in patients with haemorrhagic stroke, who presented to the local emergency department. These biomarkers were compared to values measured in patients with ischaemic stroke. **Results:** Eight male patients with HS (mean age 67.5 years [SD 12.7]) were compared to 47 men who presented with ischaemic stroke (mean age 69.5 years [SD 12.7]). There was no difference between the 2 groups in regard with *df* (1.766±.066 versus 1.759±0.049, p=0.70) or TGP (224±35 seconds versus 220±65, p=0.86). Fibrinogen (3.5±0.7 versus 3.6±0.7, p=0.63) and platelet count (212±57 versus 231±63, p =0.42) were also similar between the 2 groups. **Conclusion:** Patients with haemorrhagic stroke have denser and stronger clot structure as detected by *df* indicating a hypercoagulable state similar to those presenting with ischaemic stroke. The jury is still out whether this is a consequence of brain damage or an underlying hypercoagulable state with defective fibrinolysis. This has clinical implications with regard to indication and optimal timing for initiating antithrombotic therpy in such patients (HS) particulary those with high risk of future thrombotic events.

Figure 1: a typical representation of a Gel Point (GP) curve showing the change in phase angle (s being a measure od the viscoelastic response to imposed stress) for the different frequencies with respect to time. The initial response is characteristic of a viscoelatic solid accuring at the GP ius real – time clot formation time whereas the structural property of the incipient dot (in terms of its dimension) is derived from the frequency independent value of s

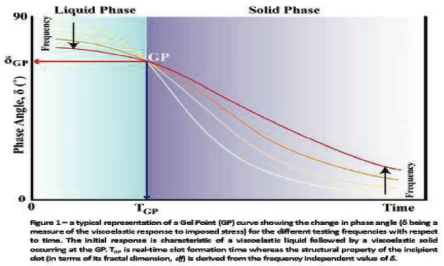


Figure 1 – a typical representation of a Gel Point (GP) curve showing the change in phase angle (δ being a measure of the viscoelastic response to imposed stress) for the different testing frequencies with respect to time. The initial response is characteristic of a viscoelastic liquid followed by a viscoelastic solid occurring at the GP. T_{GP} is real-time clot formation time whereas the structural property of the incipient clot (in terms of its fractal dimension, *df*) is derived from the frequency independent value of δ.

