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SHORT RESEARCH ARTICLE

Multiple intracerebral hematomas during SEEG recording and intradural hemorrhage after spinal tap: A case report prompting more research on collagen IV gene mutation and oral nicotine consumption as risk factors

Markus Leitinger[1,2] | **Serena Broggi**[3] | **Mathias Spendel**[4] | **Gudrun Kalss**[1,2] | **Ivan Petrović**[5] | **Herbert Krainz**[4] | **Fabio Rossini**[1,2] | **Julia Höfler**[1,2] | **Andreea Toma**[1,2] | **Giorgi Kuchukhidze**[1,2] | **Matthias Mauritz**[1,2] | **Kai-Nicolas Poppert**[1,2] | **Bernardo Crespo-Pimentel**[1,2] | **Pilar Bosque-Varela**[1,2] | **Anna Pleyers**[6] | **Patricia Ganger**[6] | **Dieter Kotzot**[6] | **Davor Lessel**[6,7,8] | **Christoph J. Griessenauer**[4] | **Eugen Trinka**[1,2,9]

[1]Department of Neurology, Neurocritical Care, and Neurorehabilitation, Center for Cognitive Neuroscience, European Reference Network EpiCARE, Christian Doppler University Hospital, Paracelsus Medical University, Salzburg, Austria

[2]Neuroscience Institute, Center for Cognitive Neuroscience, Christian Doppler University Hospital, Paracelsus Medical University, Salzburg, Austria

[3]Neurology and Stroke Unit, ASST Sette Laghi Hospital, Varese, Italy

[4]Department of Neurosurgery, Christian Doppler University Hospital, Paracelsus Medical University, Salzburg, Austria

[5]Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia

[6]Department of Human Genetics, Landeskrankenhaus University Hospital, Paracelsus Medical University, Salzburg, Austria

[7]Institute of Human Genetics, University of Regensburg, Regensburg, Germany

[8]Institute of Clinical Human Genetics, University Hospital Regensburg, Regensburg, Germany

[9]Medical Informatics, and Technology, Institute of Public Health, Medical Decision Making and Health Technology Assessment, University for Health Sciences, Hall in Tyrol, Austria

Correspondence
Markus Leitinger, Department of Neurology, Neurocritical Care, and Neurorehabilitation, Center for Cognitive Neuroscience, European Reference Network EpiCARE, Christian Doppler University Hospital, Paracelsus Medical University, Ignaz-Harrer-Straße 79, Salzburg 5020, Austria.
Email: ma.leitinger@salk.at

Abstract

Intracerebral hemorrhages (ICH) during implantation of stereo-EEG electrodes are rare. The impact of tobacco-free nicotine consumption on periprocedural bleeding is uncertain. We present a 20+ year-old man with drug-resistant epilepsy who underwent stereo-EEG with 17 depth electrodes. Within a few days after insertion, the patient developed multiple ICHs in the electrode trajectories and an intradural hemorrhage after a diagnostic spinal tap. We performed the investigation of the clotting system and whole-exome sequencing (WES). WES identified a heterozygous mutation c.4698G>T, p.(Trp1566Cys) in *COL4A2* (NM_001846.4) encoding a collagen type-IV alpha-2 chain inherited

from his seemingly healthy mother. As *COL4A2* mutations had been identified in four adult patients with ICH we postulated that the identified variant presents a potential risk factor. Notably, mutations encoding other collagens have been linked to cerebral hemorrhages (*COL4A1*) and increased propensity to trigger ICH upon smoking (*COL1A2*). Our patient consumed at least 24 oral nicotine pouches (containing 11 mg nicotine each) per day. We consider the patient's *COL4A2* mutation in combination with his substantial nicotine consumption as likely predisposition to multiple ICHs precipitated by stereo-EEG. Patients with nicotine consumption and any collagen mutation may have a substantially higher risk for hemorrhagic complications in SEEG and other neurosurgical procedures.

Plain Language Summary: A young man with drug-resistant epilepsy experienced multiple intracerebral hemorrhages after implantation of SEEG electrodes for presurgical evaluation and concomitantly a intradural hemorrhage after a lumbar spinal tap. A collagen IV mutation of unclear significance and heavy use of oral nicotine pouches were the only potential risk factors identified. As collagen mutations were previously described risk factors and smoking in particular worsens the bleeding risk in collagen mutations, further research is warranted to prevent hemorrhages in neurosurgical procedures. Nicotine consumption in any form is a preventable risk factor.

KEYWORDS

coagulopathy, COL4A2, patient safety, Skruf, tobacco-free nicotine pouch

1 | INTRODUCTION

In patients with drug-resistant epilepsy and inconclusive noninvasive presurgical evaluation, stereo-EEG (SEEG) with intracerebral depth electrodes is an effective method to identify the seizure onset zone.[1] Very low complication rates demonstrate its general safety.[2–4] In a large series of 201 SEEG patients with 2510 implanted electrodes, intracerebral hemorrhages (ICH) occurred in 11% of implants or 0.9% of electrodes.[4] Lumbar hemorrhage within 30 days after a spinal tap occurred in 0.20% and 0.23% of patients without and with coagulopathy, respectively, in a study investigating 83 711 individual lumbar punctures.[5] Therefore, multiple bleedings both in brain and spine raise the suspicion of a relevant disposition to hemorrhagic complications.

The association between an increased risk of ICH and tobacco smoke was recently reviewed by Cho et al. who identified eight studies with a significant hazard ratio for tobacco smoking.[6] Over the last years, oral tobacco-free nicotine products entered the market with the aim to deliver nicotine without exposing a person to risks associated with smoking or oral tobacco.[7]

Key points

- A young man with drug-resistant epilepsy underwent SEEG and developed multiple intracerebral hemorrhages and a hemorrhage after spinal tap.
- The only risk factors were a collagen COL4A2 mutation encoding collagen type-IV alpha 2 chain, and substantial oral nicotine consumption.
- Collagen mutations may increase the risk for cerebral hemorrhages, yet are not detectable in standard coagulation tests.
- Nicotine might aggravate the effects of collagen mutations with only limited evidence so far.
- Research should focus on potential interactions between collagen and nicotine to prevent hemorrhages in neurosurgical procedures.

2 | METHODS

We performed whole-exome sequencing (WES) from whole blood validated by PCR and Sanger sequencing.[8]

The patient gave written informed consent to the anonymized publication of his medical case. Ethics approval was obtained by the Ethics Committee of the District of Salzburg, Austria (1039/2024).

3 | RESULTS

We present a man in his early twenties who underwent SEEG due to drug-resistant epilepsy. The patient received a thrombosis prophylaxis with dalteparin 5000 IU s.c. once a day at a body weight of 63 kg. The daily doses of levetiracetam were 2500 mg, lamotrigin 400 mg, cenobamate 200 mg, metamizol 1500 mg, and paracetamol 1000 mg. C-reactive protein (CRP) was normal on admission but on the second postoperative day CRP increased to 4.0 mg/dL (laboratory range <0.6), interleukin-6 (IL-6) was elevated to 75.2 pg/mL (laboratory range <7.0) with normal procalcitonin. Apart from heavy use of oral nicotine, there were no other toxic habits.

Seventeen depth electrodes (AD-TECH®, https://adtechmedical.com) were inserted into the left cerebral hemisphere with a frameless image-guided stereotactic system (VARIO-GUIDE®)[9] in general anesthesia (propofol, sevoflurane, remifentil, and rocuronium). The postoperative cerebral CT scan was normal. On postoperative Day 2, the patient developed fever (39.9°C). The neurological examination was normal on Day 2, a diagnostic spinal tap was performed. We suspected a viral infection despite a normal cell count in the CSF. However, a wide array of viral antibodies was inconclusive. An incipient bacterial infection was taken into differential diagnosis for which intravenous cefuroxime was initiated.

On postoperative Day 7, the electrodes were removed, and the antibiotic treatment stopped. On postoperative Day 11, the patient developed fever again (38.9°C). The CSF revealed 475 cells/μL of various cell types, including polymorphonuclear cells, activated lymphocytes and monocytes, and erythrosiderophages. Brain MRI revealed multiple ICHs up to 3 × 2.8 × 1.8 cm in the subacute stage equivalent to an occurrence of about 7–10 days earlier (Figure 1). In detail, there were 12 hemorrhages (>5 mm) affecting 26/172 electrode contacts (15%) on 8/17

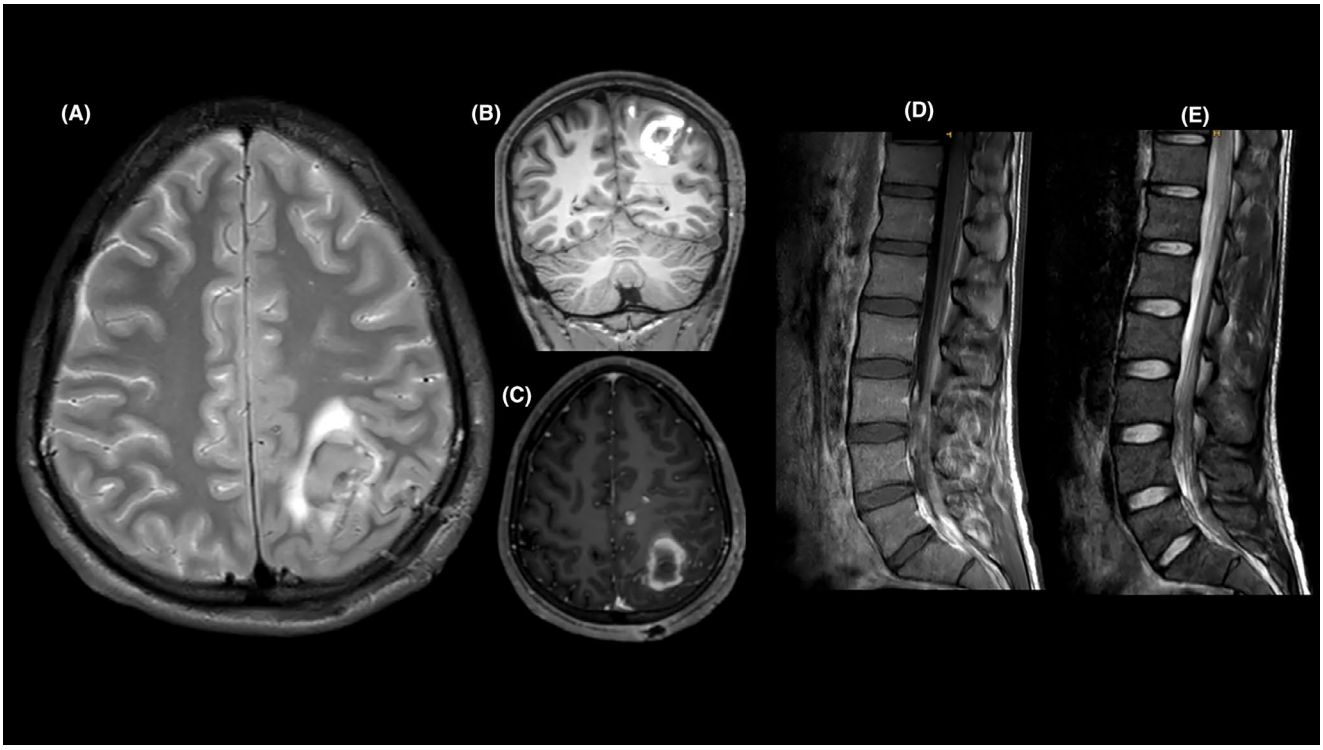

FIGURE 1 MRI scans of the patient's brain before the evacuation of the largest intracerebral hemorrhage (ICH): An axial FLAIR (A), coronal T1 (B), and axial T1 with contrast (C) show a high parietal T1 peripheral hyperintense/T2 hypo- to isointense lesion (3 × 1.8 × 2.8 cm) with peripheral edema and without pathological contrast enhancement, compatible with an early subacute (7- to 10 day-old) ICH. MRI scans of the lumbar spine: A T1 scan with contrast (D) and a T2 scan (E) show an intradural T1 hyperintense/T2 hypointense signal alteration at the L3/L4 level, without contrast enhancement, compatible with an early subacute intradural lumbar hematoma.

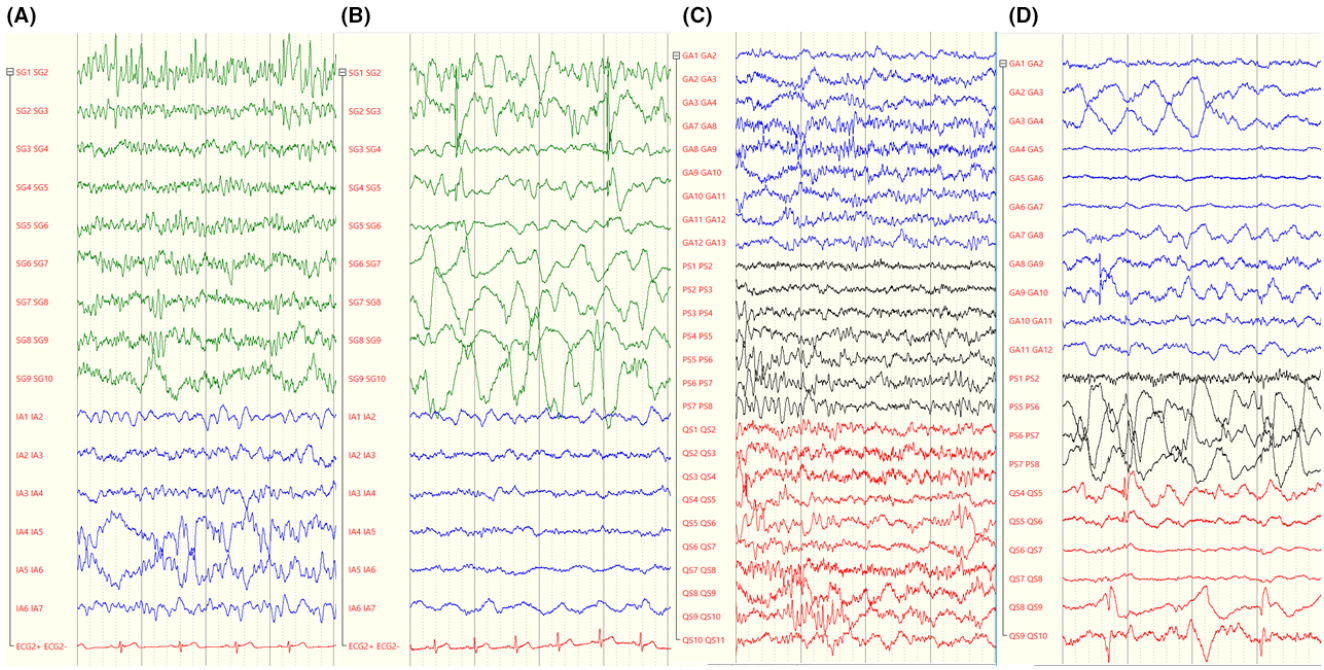

FIGURE 2 Changes in SEEG as signs of intracerebral hemorrhages. The stereo-EEG electrodes show substantially different patterns on the first postoperative day (A, C) compared with the third postoperative day (B, D), each recorded in the awake patient. Whereas fast frequencies prevail on the first postop day, slow waves predominate on the third postop day in electrodes SG, IA, GA, PS, and QS. The figure shows a bipolar montage of each SEEG electrode position connected to its adjacent neighbor electrode position. GA superior parietal lobule, inferior anterior portion; IA anterior insula; PS superior parietal lobule, superior anterior portion; QS superior parietal lobule, superior posterior portion; SG superior parietal lobule, middle portion. (low frequency filter 0.53 Hz, high frequency filter 400 Hz.)

electrodes (47%), all ICHs were in the trajectories of the depth electrodes.

Clinically, the patient demonstrated mild weakness of the right leg, compatible with the large left sided parietal ICH with compressive effect on the left motor cortex. The other, considerably smaller ICHs had no relevant mass effect on the brain and were clinically inapparent. Therefore, the largest ICH was evacuated and specimens were sent to microbiological workup which revealed no germ. The postoperative CT scan showed satisfactory hematoma evacuation and no expansion of the smaller ICHs.

A calculated antibiotic treatment with meropenem was started. A concomitant clostridium difficile infection was treated with oral vancomycin.

Due to pain in both dorsal thighs, a lumbar spine MRI was performed on the twelfth postoperative day and revealed an intradural hemorrhage in an early subacute phase, compatible with the previously performed first lumbar puncture on postoperative Day 2. Surgical intervention was not required.

The patient fully recovered clinically, neurological examination and neuropsychological testing before discharge were both normal. Follow-up brain MRI scans showed proper ICH resorption.

As an indirect marker for the time of occurrence of ICHs, significant changes of SEEG-recordings occurred between the first and the third postoperative day on the respective leads (Figure 2).

The unexpected occurrence of multiple hemorrhages during SEEG triggered a comprehensive workup. Extended coagulation studies were unremarkable (supplemental material). Past medical history of neurodermitis was not considered relevant. The family history was negative for epilepsy and coagulopathies. Remarkably, the patient consumed at least 24 (one box) tobacco-free nicotine pouches (11 mg nicotine each) on a daily basis (https://www.superwhite.at). WES did not identify any mutation in genes linked to epilepsy. However, we identified a heterozygous mutation c.4698G>T, p.(Trp1566Cys) in *COL4A2* (NM_001846.4) encoding a collagen type-IV alpha-2 chain, which was inherited from his unremarkable mother. The patient's mother gave unremarkable birth to three children as a non-smoker but has been smoking six cigarettes per day for 5 years. She underwent no major surgeries.

The mutation was not identified in 807 068 individuals according to the gnomAD v4.0.0 database (gnomad.broadinstitute.org), it affects the highly conserved Tryptophan within the beta-strand of the C4 domain.

4 | DISCUSSION

The occurrence of multiple intracerebral hematomas during SEEG recording and a symptomatic lumbar intradural hematoma after a spinal tap in our patient could not be explained by thorough blood coagulation studies.[2–5] ASMs and anesthetics were not associated with any bleeding complication in a PubMed search.

Initially, we regarded the high daily oral nicotine consumption as a relevant risk factor. In a randomized, controlled, crossover clinical study investigating nicotine pharmacokinetics, the area under the curve up to 6 h (AUC 0-6 h) was 25.2 ng.h/mL for a cigarette and 1.5 fold for an 8 mg nicotine pouch (Skruf: 39.0 ng.h/mL).[7] We estimated the patient's nicotine consumption equivalent to approximately 50 cigarettes per day.

As opposed to tobacco smoking, a moderate-to-high oral tobacco-free nicotine intake has not been associated with ICH so far. Smokeless tobacco was identified as a risk factor for ischemic stroke in young patients[10] whereas no association between oral tobacco and stroke was found in a pooled analysis of eight prospective Swedish cohort studies.[11] Most studies on nicotine or tobacco focused on the analysis of blood components. However, bleeding might be caused by changes of the vessel wall (e.g., the basement membrane) which cannot be detected in blood investigations.

In rats, the risk of enlargement of collagenase-induced ICHs in the striatum was increased by nicotine exposure,[12] which pointed to the pathophysiological roles of collagen and nicotine. In a large study investigating 227 Han Chinese patients, a collagen mutation of *COL1A2* (rs42524) was associated with a 2.57 fold (95% CI 1.45–4.63) increased risk of ICHs compared with matched controls using a dominant model.[13] Importantly, smoking accentuated the risk of ICH, which might be a relevant association as well in our patient who did not smoke but consumed high doses of oral nicotine.[13]

Therefore, the second main investigation regarded the patient's *COL4A2* mutation. Even though there is considerable evidence for an association of *COL4A1* and ICH, data are sparse for *COL4A2* mutations.[14] Physiologically, two pro-alpha 1(IV) chains encoded by *COL4A1* form trimers that include in addition a pro-alpha2(IV) chain encoded by *COL4A2* which form together the major component of the basement membranes in several tissues.[15] A case series of four adults with *COL4A2* mutations was published in 2012.[16] Mutation of *COL4A2* (c.3368A>G leading to E1123G, exchange of glutamate by glycine in exon 37, which is part of the triple helix formation) led to spontaneous ICH in two non-Hispanic patients.[15] A 45-year-old Hispanic patient with hypertension suffered from ICH (c.3448C > A,Q1150K, glutamine tolysine, exon 37) [Jeanne-M,2012]. Another mutation (c.5068G > A, A1690T, alanine to threonine, exon 48) was found in an African American man.[15] All three mutations were shown to impair the secretion of *COL4A2* and *COL4A1* in an in vitro functional assay.[15] In animal models, *COL4A2* mutations caused less severe ICHs than *COLA4A1* mutations, probably due to the 2:1 ratio of *COL4A1:COL4A2* in *COL4A1/A2* hetero-trimers.[15] The mutation in our patient c.4698G>T, p.(Trp1566Cys) has not yet been described. However, any interference with the physiological generation of collagen may interfere with proper function.

The p.(Trp1566Cys) in *COL4A2* in our patient is a missense variant resulting in amino acid substitution from highly conserved, non-polar Tryptophan to polar Cysteine, thus exhibiting a shift in polarity.

This missense variant is located within the globular, C-terminal, noncollagenous domain (NC1) domain, that is necessary to for triple helix formation and its function.[16] Typically, NC1 domains, and also the COL4A2 NC1 domains, consist of 12 Cysteines that are involved in disulfide bonds, thereby regulating the stability of the protein. Additional, Cysteine residue within the NC1 domain could therefore interfere with its stability.[17]

Further evidence that this missense variant might be harmful on an organismal level comes from a large sequencing dataset, gnomAD V4, where this variant has not been identified in more than 800.000,00 analyzed individuals. We thus postulate that the combination of oral nicotine with affected trimerization might be the cause of the hemorrhagic complications here. Clearly, this hypothesis should be further investigated in appropriate models.

This study has several limitations. First, the pure association of a genetic variant—to date classified as a variant of unknown clinical significance class 3 according to the American College of Medical Genetics and Genomics (ACMG)—does not prove any causative role. Without identifying further similar cases harboring the identical mutation, functional analyses are needed to confirm its causality. Ideally, knock-in mice models would be generated and analyzed. However, this paper should encourage human genetic analysis if ICHs occur during SEEG.

Second, it remains unclear whether there is a class effect among collagen mutations with respect to their predisposition to ICHs and whether this risk is increased by oral nicotine or tobacco use.

Third, the patient was operated in the CNS (implantation of depth electrodes) indicating the need for a precipitating event. However, the very early occurrence of both the multiple ICHs during SEEG and the lumbar intradural hemorrhage after a diagnostic spinal tap suggests a stronger predisposition to a bleeding disorder.

In conclusion, our findings should be regarded as a consideration that merits further research and will need appropriate preclinical and clinical studies to address the contribution of oral nicotine and collagen mutations to failure of hemostasis.

Our case emphasizes the so-called harmless consumption of oral nicotine products in relation to the perioperative risk of cerebral hemorrhages. This risk should be determined after a detailed history of substance consumption including oral nicotine or tobacco products. Moreover, genetic findings regarding components of the vessel wall, for example, collagen in the basement membrane, could be considered as relevant risk factors. Studies on hemorrhagic complications in SEEG should include inquiries about nicotine consumption in any form and any collagen mutations. Research should focus on the interactions between collagen variants of unknown significance and oral nicotine or tobacco consumption with respect to hemorrhagic complications.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Markus Leitinger https://orcid.org/0000-0001-8552-6762
Serena Broggi https://orcid.org/0000-0003-3987-9772
Gudrun Kalss https://orcid.org/0000-0002-4311-1734
Ivan Petrović https://orcid.org/0009-0006-0409-3701
Julia Höfler https://orcid.org/0009-0001-7593-0056
Giorgi Kuchukhidze https://orcid.org/0000-0001-6899-8506
Matthias Mauritz https://orcid.org/0000-0002-5204-393X
Bernardo Crespo-Pimentel https://orcid.org/0000-0002-8965-8081
Eugen Trinka https://orcid.org/0000-0002-5950-2692

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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