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Case Report

What about cerebral venous sinus thrombosis? A series of three autopsy cases

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ABSTRACT

Cerebral venous sinus thrombosis (CVST) is an uncommon cerebrovascular disorder that gained massive media attention in 2021, when an association between COVID-19 and its vaccines was found in several reported cases, raising the suspicion of a causative relation that is still debated.

Three cases of CVST unrelated to COVID-19 are reported in this article to highlight the difficulty in the early recognition and management of this condition, as it occurs in a variety of diseases with different clinical and pathological manifestations.

When the diagnosis cannot be achieved in the clinical setting, the role of the pathologist becomes essential in the determination of the cause of death and in the identification of the etiology of CVST.

During the autopsy, coordination between the physician and the forensic pathologist is crucial to correlate the clinical presentation with the pathological picture.

1. Introduction

Cerebral venous sinus thrombosis (CVST), cerebral venous and sinus thrombosis or cerebral venous thrombosis (CVT), is the presence of a blood clot creating an obstruction in the dural venous sinuses, the cerebral veins, or both which represent the drainage system of the brain [1].

It is an unusual cause of stroke and can be easily missed or misdiagnosed in the clinical setting [2,3].

During 2021, this condition attracted the attention of the scientific community, when some cases of CVST associated to both COVID-19 and its vaccines were reported [4-8].

The case series presented in this article is not related to COVID-19, but it is still relevant in the portrayal of the medical challenge represented by CVST, since it occurs in a variety of diseases with different clinical and pathological manifestations. For each patient, the clinical history was reconstructed from the medical charts. The autoptic examination and the histological study were carried out in the Medico-Legal Section of the Department of Anatomical, Histological, Forensic Medicine and Orthopedics Sciences, Sapienza University of Rome in the suspicion of medical malpractice.

The aim of this study is to focus on the forensic pathologist’s approach to CVST, since the evaluation both from a clinical and a autoptic perspective is quite complex. In the case series presented in this paper, the clinical pictures were extremely complicated and the review of the medical charts together with the anatomo-pathological findings were crucial in the determination of the cause of death.

2. Case series

2.1. Case 1

A 33-year-old woman, 34 weeks pregnant with twins, arrived at the hospital for a scheduled ultrasound. After careful clinical examination, she was diagnosed with acute centralization of blood flow, and a C-section was scheduled for the next day, while prophylaxis with LMWH (Low Molecular Weight Heparin) was initiated. She underwent the procedure without significant complications and the babies were born in good clinical conditions. 5 hours later she started experiencing blurred vision, accompanied by a rise in blood pressure (180/110) and oliguria. Blood analysis revealed anemia, thrombocytopenia and elevated liver enzymes, with a sharp rise in bilirubin and LDH (Table 1).

An MRI was performed, which showed the presence of a thrombus in the dural sinuses, diffuse ischemic leukoencephalopathy and cerebral
edema. Considering the laboratory and radiological analysis, Protamine Sulfate and Antithrombin III were administered together with fresh frozen plasma and packed red blood cells in the suspicion of a Thrombotic Thrombocytopenic Purpura (TTP).

Since HELLP (Hemolysis, Elevated Liver enzymes, Low Platelets) syndrome was included in the differential diagnosis, the therapy was implemented with Nifedipine, Mannitol, Betametasone, Urapidil, Clonidine and Ranitidine to treat the hypertension and reduce the intracranial pressure.

Despite the continuous monitoring and the strict therapeutic regimen, a GCS of 8 was reported in the following days, accompanied by intracranial hypertension. Clonidine and Ranitidine were implemented with Nifedipine, Mannitol, Betametasone, Urapidil, Protamine Sulfate and Antithrombin III were administered together with fresh frozen plasma and packed red blood cells in the suspicion of a Thrombotic Thrombocytopenic Purpura (TTP). However, due to the patient’s poor response to the therapeutic procedures, her clinical conditions rapidly deteriorated. After suspension of sedative therapy, no response to verbal, tactile or motor stimuli was detected; an urgent EEG showed no signs of organized brain electrical activity and signs of pathophysiological compromise. The patient did not respond adequately to the procedure and shortly after she was declared brain dead, as she met the criteria of persistent coma, absence of brainstem reflexes, and lack of ability to breathe independently.

### 2.2. Autopsy

To establish the cause of death, an autopsy was conducted in the suspicion of medical malpractice. At brain examination, the parenchyma appeared strongly edematous, while upon sectioning the dural venous sinuses, a thrombus extending from the superior sagittal sinus (SSS) to the confluence of sinuses and the transverse sinuses bilaterally was detected (Fig. 1).

Genital tract examination revealed the presence of a mild hemorrhage both within the uterus and the Fallopian tubes with bilateral hematosalpinx (Table 2).

#### Table 1. Laboratory analysis for Case 1 (N.V. normal values).

| Parameter                  | Admission | Onset of | Last registered |
|----------------------------|-----------|----------|----------------|
| Hemoglobin (g/dL)          | 12-16     | 12.3     | 7.20           | 9.70          |
| Erythrocytes (10^12/L)     | 4.20-5.40 | 3.76     | 2.23           | 3.07          |
| Hematocrit (%)             | 37-47     | 35.7     | 21.20          | 30            |
| Platelets (10^3/μL)        | 130-400   | 125      | 18             | 31            |
| LDH (U/L)                  | 220-460   | 360      | 2401           | 1058          |
| AST (U/L)                  | < 31      | 18       | 306            | 41            |
| ALT (U/L)                  | < 31      | 10       | 267            | 44            |
| Total Bilirubin (mg/dL)    | < 1.1     | 0.58     | 1.5            | 1.1           |

Fig. 1. Case 1 Superior Sagittal Sinus. In situ incision of the SSS with a longitudinal section of the vessel to expose the thrombus.

**2.3. Histological examination**

At microscopic examination of the brain, the microcirculation appeared congested with areas of intraparenchymal hemorrhage and edema.

The thrombus found in the SSS consisted of erythrocytes clusters embedded in a fibrin network with polymorphonuclear cells infiltrates. Similar microscopic findings were discovered upon histological examination of the Fallopian tubes and the uterus, with signs of myometrial hemorrhage and infarcted foci at the level of the submucosa of the birth canal.

Considering both the clinical and the pathological picture, the medical examiner established that the cause of death was a severe CVST in the setting of a hypercoagulable state. The histological findings are summarized in Table 2.

#### 2.4. Case 2

A 45-year-old woman with a history of deep venous thrombosis, congenital valvulopathy which had required mitral valve replacement, and heart failure with subsequent implantation of a dual-chamber cardiac defibrillator, arrived at the hospital for an urgent heart transplant. The procedure was successful without relevant intra-operative complications.

On the first day after the surgery, the patient was stable; however, on the following day, she started experiencing signs of respiratory failure associated with severe headache, and shortly after she became comatose. Therefore, she was sedated and intubated for mechanical ventilation. Blood tests showed an increase in amylase, lipase and transaminases, coupled to metabolic acidosis. The laboratory analyses performed in the following days are summarized in Table 3; a progressive increase in D-dimer values was detected, while platelets, PT, PTT, fibrinogen, and anti-thrombin showed consistent oscillations (Table 3). Therefore, the patient underwent multiple transfusions in order to stabilize the hematological impairment.

Upon radiological examination with an abdominal CT, the presence of edematous pancreatitis with associated retroperitoneal fluid, multiple splenic infarcts, and bilateral renal hypoperfusion was demonstrated. A head CT showed evidence of subcortical ischemic foci with severe edema and brain herniation, with no signs of CVST. After a neurological consultation, an MRI was scheduled for the following day to clarify the extension and the entity of the cerebral involvement, while Mannitol and immunosuppressive drugs were administered to reduce the intracranial pressure and minimize the immunological response. The patient did not respond as expected to the therapeutic procedures and her clinical conditions rapidly deteriorated. After suspension of sedative therapy, no response to verbal, tactile or motor stimuli was detected; an urgent EEG showed no signs of organized brain electrical activity and she was declared brain dead before the MRI could be performed.

#### 2.5. Autopsy

To determine the cause of death, an autopsy was scheduled for the following days. At brain examination, the dura mater appeared thickened at the level of the SSS; the venous lumen was occluded by a thrombus which was tightly adherent to the vascular wall, with involvement of the sinus confluence, the transverse sinus, and the sigmoid sinuses (Fig. 2 a).

The brain parenchyma was edematous, and multiple infarcted areas were detected at the level of the parietal lobe (Fig. 2 b).

From a macroscopic point of view, the transplanted heart showed no signs of pathophysiological compromise. Upon gross inspection of the abdominal viscera, the diagnosis of pancreatitis was confirmed, while the kidneys were reduced in size.
Signs of infarction and surrounding congestion of the spleen parenchyma were present (Table 2).

### 2.6. Histological examination

The transverse section of the SSS revealed complete occlusion of the lumen as a result of erythrocytes and fibrin deposition that led to the formation of a thrombus; the degree of reorganization of the deposits suggested that thrombus formation had occurred 8–10 days before the exitus (Fig. 2 c-d). Parietal lobe microscopic examination showed signs of edema and congestion, with the presence of diffuse hemorrhagic foci (Fig. 2 e).

The histopathological findings of the lung specimens showed thrombotic occlusion in the arterial vasculature up to the smaller branches, with ischemic foci in the lung parenchyma.

Autolysis and liquefaction of the pancreas were demonstrated by the presence of calcifications, necrosis, fibrosis, and lymphocytic infiltration in the parenchyma, along with focal hemorrhagic areas.

The renal cortex was deprived of its nuclei, with glomerulo-tubular ischemia and interstitial nephritis with monuclear cells infiltrates.

### Table 2

Overview of macroscopic and histological findings (L: left, R: right, - missing data or no significant alteration).

| Organ                  | Case 1 | Case 2 | Case 3 |
|------------------------|--------|--------|--------|
| **Weight (grams)**     |        |        |        |
| Brain                  | 1475   | 1507   | 1538.5 |
| Heart                  | 372    | 618    | 531.5  |
| Lungs                  | L:945  | L: 276 | L: 980 |
|                        | R:1020 | R: 325 | R:1103 |
| Liver                  | 2190   | –      | –      |
| Pancreas               | –      | –      | –      |
| Spleen                 | 309    | 297    | 547    |
| Kidneys                | L: 185 | L: 99  | L: 224.5|
|                        | R: 172 | R: 110 | R: 219 |
| Genital tract          | –      | –      | –      |
| (Uterus and Fallopian   |        |        |        |
| Tubes)                 |        |        |        |

### Table 3

Coagulation panel in Case 2 (N.V. normal values).

|                   | N.V. | Admission | Onset of neurological signs | Last registered values |
|-------------------|------|-----------|-----------------------------|------------------------|
| Platelets (10^3/µL) | 150–450 | 146 | 121 | 129 |
| PT (INR)          | 0. – 1.2 | 2.55 | 1.76 | 1.06 |
| PTT (sec.)        | 24–40 | 69.2 | 27.3 | 24.1 |
| Fibrinogen (mg/dL)| 150–250 | 125 | 686 | 456 |
| D-Dimer (ng/mL)   | < 500 | 2389 | 6047 | 8607 |
| Antithrombin (%)  | 80–130 | 50 | 146 | 119 |
The spleen parenchyma was affected by diffuse infarcted areas. Given the extension of the thrombus and the anatomo-pathological signs of systemic thrombosis this was recognized as the ultimate cause of death in a patient with severe, complicated pancreatitis with evidence of multiorgan failure (Table 2).

2.7. Case 3

A 34-year-old male arrived at the Emergency Room (ER) complaining of an episode of severe headache lasting more than a week without significant response to pharmacological treatment with triptans. No clinically relevant pre-existing conditions were reported. An urgent CT scan was performed, which showed no signs of hemorrhage or masses, aside from radiological evidence of previously diagnosed chronic sinusitis. He was discharged but the following week he returned to the ER with the same symptoms and inconclusive exams.

Two weeks after the initial presentation, he arrived at the ER in critical conditions due to a sudden loss of consciousness that caused him to fall and injure his head, resulting in a scalp laceration at the level of the frontal region; the patient was unconscious, in a convulsive status.

Blood analysis showed neutrophilic leukocytosis and thrombocytosis, while toxicological tests were negative.

Head CT revealed diffuse hypodensity of the cerebral parenchyma with swelling and compression of the ventricular system associated to two hemorrhagic foci on the median left brainstem accompanied by herniation of the cerebellar tonsils. Widespread inflammation of the paranasal sinuses was also evident, with thinning and hypodensity of the maxillary bones. Cerebrospinal fluid (CSF) PCR analysis was inconclusive, with a clear liquor characterized by 12 cell/micromol, lymphocytes exocytosis, and rare polymorphonuclear cells.

Head CT performed on the following day demonstrated transtentorial herniation of the brainstem and cerebellar tonsils; the IV ventricle was undetectable, and the rest of the ventricular system showed an overall reduction in volume.

An MRI showed extensive cerebral edema with T2-Flair signal...
enhancement and diffuse venous congestion. No sign of CVST was recognized upon radiological investigations. An EEG showed signs of uncontrolled electrical activity consistent with the clinical picture of a severe encephalopathy, with prominent involvement of the right hemisphere. Shortly after, a perfusion CT showed cessation of blood circulation; therefore, the patient was declared brain dead.

Autopsy.

At skull examination, the dural venous sinuses appeared strongly congested (Fig. 3 a) and upon in situ incision of the SSS along its major axis, a thrombus obstructing the posterior two-thirds of the sinus was found. The thrombus extended from the SSS to the straight sinus and the transverse sinuses bilaterally (Fig. 3 b–d). The leptomeningeal vessels were also congested with various smaller blood clots. The lateral ventricles were small in size containing a reduced amount of clear CSF. An area of hemorrhagic infarction was detected at the level of the pons. The anatomo-pathological findings of the organs are summarized in Table 2.

Histological Examination.

Microscopic examination of the SSS and the dura mater showed an occluding thrombus attached to the vascular wall and characterized by alternating layers of erythrocytes, fibrin, and PMN cells infiltrates (Fig. 4). Microscopic inspection of the brain parenchyma confirmed the presence of edema and circulatory congestion, with extensive infiltration of lymphocytes (Fig. 5 a). Similar pathological findings were recognized at the level of the kidneys and the heart, raising the suspicion of a systemic lymphocytic vasculitis with predominant cerebral involvement (Fig. 5 b-c).

The microscopic analysis was crucial in the determination of the cause of death, i.e. CVST as a result of a systemic vasculitis, since no additional signs of inflammatory vascular processes were detected in the clinical setting.

3. Discussion

Thrombosis of the cerebral veins and sinuses is a rare but significant cause of stroke especially in young adults, accounting for 0.5–1.0% of stroke admissions, with an estimated incidence of 3–4 per 1 million people annually [9–10]. On the other hand, accurate epidemiological data on the occurrence CVST are not available since this condition is frequently missed, as it can mimic other acute neurological conditions, but it was found in 9.3% of one consecutive autopsy series [11]. The causes of CVST can be genetic, where heritable thrombophilias include mutations on factor V Leiden and the G20210A prothrombin genes, together with antithrombin, protein C and S deficiency [12]. The most common acquired prothrombotic states are pregnancy, the puerperium and oral contraceptives use, increasing the risk of CVST among women of childbearing potential by three-fold [1]. Additional risk factors for the
development of CVST include obesity, low flow states, dehydration, infections, antiphospholipid antibody syndrome, and malignancy [13–14]. In patients aged over 55 years, CVST is equally prevalent between the sexes, and malignancy is a frequent cause [15]. Infection of the central nervous system, either from hematogenous dissemination, direct contamination or spread from adjacent structures, like in otitis media or sinusitis, is another important cause of CVST [16–17]. In 80% of cases a definite risk factor or cause of CVST can be recognized, while the rest are classified as idiopathic [18].

Case 1 represents a typical picture of CVST, as it occurred in a young woman, during puerperium, in the context of severe pre-eclampsia complicated by a hypercoagulability state with associated disseminated intravascular coagulation (DIC).

Case 2 is characterized by pre-existing congestive heart failure coupled to heart transplant which are both important causes of hemodynamic instability and localized and systemic inflammation, as described by the concerning literature [19–20]. In this case, CVST occurs in the setting of a multi-systemic organ damage with involvement of the kidneys, spleen, and liver.

In Case 3, the lymphocytic vasculitis diagnosed during the post-mortem examination was the causative event of CVST. This is an atypical cause, with a peculiar clinical and pathological presentation [21].

In all three cases, the presence of a pre-existing cause of coagulopathy was excluded since the clinical picture was suggestive of a recently acquired condition; therefore, thrombophilia screening panels were not performed.

CVST represents the terminal event of a systemic pathophysiological process that can be initiated by several conditions and diseases by establishing a hypercoagulability state. These result in significant brain injury and, in approximately 10% of cases, death of the patient [22–23].

Thrombus formation in the cerebral vasculature causes occlusion of the affected vessels with obstruction of blood flow and subsequent accumulation of fluid in the venous sinuses and dural veins, thus resulting in a pressure rise. Localized and diffuse edema, venous infarction and impaired reabsorption of CSF ultimately lead to venous stasis, damage to the blood brain barrier (BBB) and further vasogenic

Fig. 4. Case 3 histological specimens of the SSS thrombus. a) SSS thrombus microscopic structure with erythrocytes, fibrin deposits and PMN cells infiltrates - note the contact with the dural sinus wall with minimal PMN cells infiltrates. (20x) b) Degree of re-organization of the thrombus which allows to give an estimation on the age of the thrombus, approximately 8–10 days (compare with Fig. 5c) (20x).

Fig. 5. Case 3 histological examination of brain parenchyma and meninges. a) Edema, congestion with extensive hemorrhagic area. (10x) b) Thrombosis of the smaller branches of the meningeal vasculature, surrounded by intense lymphocytes cells infiltrates. (10x) c) Focus on the perivasal lymphocytes cells infiltrates that extends up to the vascular wall (10x).
edema [5,24]. These processes are also associated to reduced cerebral perfusion and accumulation of waste products and inflammatory mediators, which produce additional parenchymal damage.

The mechanisms of CVST formation and associated damage explain the pathological picture that can be observed during the autopsy, which is usually characterized by the co-existence of multiple morbid conditions that reinforce the assumption of a multi-systemic involvement.

The three cases presented in this paper are overall very heterogeneous among themselves, with extremely different pre-existing conditions. The common feature is represented by the discovery of a thrombus extending from the SSS to transverse sinuses, the sigmoid and the rectum sinuses during the autopsy, which was identified as the cause of death in all three cases. An additional autopsic finding that was constant in this case series was the massive cerebral edema detected during the opening of the cranial vault.

The clinical presentation of CVST is complex, with a wide range of possible signs and symptoms that depend on the involved sinus, the entity of the occlusion and the associated clinical conditions. The chief complaint in the clinical setting is usually an unrelenting, constant headache of variable duration that is unresponsive to common over-the-counter analgesics and triptans [9]. Focal neurological deficits, seizures and visual impairment are other common signs.

In the case series described in this paper, the first woman presented with blurred vision which is also associated to HELLP syndrome, the second patient was sedated for most of the time after the surgical intervention, while the neurological signs reported by the patient in Case 3, i.e., severe headache and ultimately seizures, were most likely the result of the underlying CNS inflammation and the traumatic brain injury.

Urgent neuroimaging is always required in the setting of suspected CVST, where a head CT scan without contrast is the fastest way to acquire useful brain images [25]. In pregnancy, MRI is the preferred choice. Venous hyperdensity represents the most specific sign and can be accompanied by edema, hemorrhage, and in severe cases, infarction. Blood analyses include routine hematocrit, chemistry and coagulation panel, where a D-dimer test can be included in the diagnostic workup [9,18,26].

The angio-MRI performed in Case 1 became diagnostic only at a late stage of the thrombosis, while remaining inconclusive in the rest of the case series. In both Case 2 and Case 3 no radiological diagnosis of CVST was obtained, as no specific signs were detected during the instrumental procedures; moreover, venous congestion was widespread in both cases.

Sometimes, CVST is clinically silent until its late stages and a definite diagnosis can only be achieved during autopsy, where inspection of the dural sinuses, section of the cerebral vessels and parenchyma and sampling of the pathological findings is crucial in the post-mortem evaluation. The autopsy is a fundamental step also in the identification of the etiology when this cannot be established in the clinical setting, due to the presence of confounding factors like limited time and numerous coexisting conditions [11].

For what concerns our small but representative sample, the extension and the distribution of the cerebral thrombosis were similar among the three cases, where the SSS was the most affected portion. Despite the similar cerebral venous involvement, the clinical picture was considerably different, with diverse signs, symptoms, and etiologies. The cerebral edema had been detected in all these cases, due to its tight association and self-reinforcing mechanism with respect to the pathological CVST. It should be clarified that the three patients experienced a systemic involvement with multi-organ damage, so CVST was not of primary origin.

The cases presented in this paper are paradigmatic of the difficulty both in the early recognition of CVST and in the differential diagnosis in the setting of the autopsy to identify the cause of death. As previously mentioned, cerebral thrombosis is the result of an underlying disease, therefore it is difficult to discriminate whether it represents the cause of death or just an associated peri-mortem phenomenon with little or no significance in the determination of death. The forensic pathologist must reconstruct the sequence of pathological events that lead to the exitus of the deceased, while considering that most of the diagnostic investigations conducted on the living cannot be performed on the dead. Along with the recognition of the relevant pathological conditions and specimens, other plausible causes must be excluded to confirm that, in fact, CVST was the cause of death. Coordination between the physician and the forensic pathologist, together with thorough study and review of the hospital charts is crucial to correlate the clinical presentation with the anatomo-pathological picture. Histological sampling and examination of biological specimens is fundamental to confirm the thrombotic nature of the specimens and to estimate the age of the thrombus based on the degree of organization, since the only constant feature in the range of clinico-pathological conditions that result in CVST is represented by the microscopic appearance of the thrombus correlated to the massive cerebral edema [27].

In Case 1, the diagnosis was achieved in the clinical setting but still warranted further confirmation due to the difficult conditions of the patients during her last days. In Case 2 and Case 3, CVST was discovered during autopsy, and it was identified as the cause of death, since the pre-existing conditions alone were not severe enough to cause the exitus of the patient.

Therefore, in situ incision of the dural venous vasculature is recommended in case of high clinical suspicion of CVST, especially in young patients with cerebral edema. Alternatively, in toto removal of the dura mater together with the SSS, the inferior sinus, the rectus sinus, the transverse sinuses, the sigmoid sinuses and the cavernous sinuses is advised to perform formalin fixation and later organ inspection, coupled to histological examination.

The subject presented in this study has recently gained media attention, due to its association with COVID-19 and its vaccines [4–8]. In the past few months, with the increasing rate of vaccination, numerous research programs and reviews aimed to the recognition of the pathophysiological process that could explain the connection between CVST and COVID-19 vaccines were published; the discussion between experts has risen further questions and doubts, where some studies supported the hypothesis of a correlation between the two events, and others were more cautious [28–30].

The link between VaxZevria/Astrazeneca and to a lesser extent Pfizer-BioNTech and Moderna COVID-19 vaccines and rare events of CVST has risen an increasing interest with respect to the pathological findings related to this condition that are ultimately evaluated by the forensic pathologist [31–32].

None of the cases presented in this paper have any connection with either the disease or the vaccine, but they are still relevant since, according to the Authors’ experience, the occurrence of undiagnosed or undiscovered CVST in the autopic setting is uncommon.

4. Conclusion

CVST in the setting of multisystemic diseases requires an exhaustive diagnostic workup in the clinical context for early recognition and prompt treatment of the underlying condition(s). When this cannot be achieved, a thorough autopsic examination is essential in the determination of the manner of death and, in some cases, to recognize whether medical malpractice has ensued or not.

As previously highlighted in this paper, the major difficulty is represented by the wide array of clinical and pathological findings, where none are specific for CVST, except for the presence of a thrombus associated to cerebral edema.

There is a vast literature concerning the phenomenon of CVST; nonetheless, future studies should focus on the understanding of the most commonly associated conditions and the recognition of constant features. While searching for data and information about the matter, little to no studies were dedicated to the anatomo-pathological aspects of the disease.
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6. Availability of data and material

N/A.

7. Code availability

N/A.

8. Authors’ contribution

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by LT, DP, PEYP and AMM. VP and MS provided the medico-legal reports and clinical charts for two cases. Prof. CC coordinated the drafting of the article. All authors read and approved the final version of the manuscript.

9. Ethics approval

N/A.

10. Consent to participate

N/A.

11. Consent for publication

N/A.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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