Dear Sir:

Reversible cerebral vasoconstriction syndrome (RCVS) is a relatively newly described neurovascular entity. The clinical outcome is generally benign, but sometimes disabling or life-threatening. Triggers for this condition are variable with a large proportion of idiopathic causes. Several informative papers had been written on this subject which include proposals for diagnostic criteria, differentiation from other cerebral vasculopathies, and imaging features.

However, the pathophysiology of the condition is still not well understood, especially in the large proportion of idiopathic cases. A leading hypothesis for the propagation of the condition attributes a significant role to vascular autoregulation disruption similarly to posterior reversible encephalopathy syndrome (PRES) but with different triggers. Early markers of the condition are needed, which would allow prompt treatment, avoid unnecessary studies and shed some light on the RCVS mechanism. Recently a salient study of 23 RCVS patients in South Korea described a phenomenon of contrast enhanced fluid attenuation inversion recovery (CE FLAIR) magnetic resonance imaging (MRI) hyperintensity in cortical sulci interpreted as blood brain barrier (BBB) disruption and showed its correlation to clinical outcome. We observed similar findings in Israeli population, and 18 out of 21 confirmed RCVS patients had exclusively posterior sulcal contrast enhancement (in the posterior occipital, parietal or cerebellar sulci) on CE FLAIR sequences (Figure 1). We also found a positive correlation between the extent of the CE FLAIR involvement and RCVS severity defined by a composite outcome score calculated for each individual patient.

We graded the severity of RCVS by a composite neurological score that included PRES like edema appearance on MRI (0, 1), clinical seizures (0, 1), subarachnoid hemorrhage (0, 1), brain ischemia (0, 1) and thunderclap headache on initial presentation (0, 1). Multivariate logistic regression analysis was used to assure that the score components were not affected by demographic or clinical variables. The score was devised according to previously described markers of RCVS severity. The grading of CE FLAIR included the composite of intensity of sulci enhancement by contrast (0, no signal; 1, for mild signal; 2, for substantial signal) with its distribution throughout the brain (1 point for each involved lobe—including cerebellar hemispheres; 0–10).

All the patients were female with a median age of 41, 17 (68%) with a non-significant prior medical history. Twenty-three patients (92%) were considered for an analysis (with available of MRI scans). Finally, 21 (85%) confirmed RCVS patients were included for the analysis. None of the patients exhibited a cellular inflammatory reaction in the CSF (Supplementary materials). All
Figure 1. Grades of sulcal contrast enhancement (arrows) in four representative reversible cerebral vasoconstriction syndrome patients according to increasing enhancement severity. (A) Enhancement score of 1. (B) Enhancement score of 2. (C) Enhancement score of 2, different anatomic locus. (D) Enhancement score of 4.

Figure 2. (A) Correlation of magnetic resonance imaging (MRI) severity score to composite neurological outcome score (Pearson's correlation analysis). (B, C) Subanalysis of MRI fluid attenuation inversion recovery (FLAIR) correlation to the degree of vasospasm. (D) Correlation of MRI timing on MRI FLAIR enhancement (Pearson's correlation analysis, negative values represent acquisition prior to development of vasospasm in days). CI, confidence interval; CE FLAIR, contrast enhanced FLAIR; TCCD, transcranial color Doppler.

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included patients underwent serial transcranial Doppler (TCD) imaging. Eighteen out of 21 confirmed RCVS patients exhibited increased CE FLAIR signal in cortical sulci (CE FLAIR score >0 in Supplementary Table 1, Supplementary materials). Sixteen of 21 patients suffered from neurological complications. In 18 out of 21 patients a putative causative trigger was isolated (Supplementary Table 1, Supplementary materials). Figure 2A shows that the composite score was significantly correlated with the enhancement severity on CE FLAIR signal (Pearson’s correlation analysis, Linear regression, $R^2=0.33$, $P=0.007$) (Supplementary materials). However, neither number of affected vessels nor maximum velocity on TCD (surrogates of vasoconstriction) were correlated with the CE FLAIR score (Figure 2B and C), Pearson’s correlation analysis, $P=0.415$ and $P=0.89$, accordingly. In addition, symptom duration (indicated by timing of MRI acquisition) was not correlated with the CE FLAIR score (Pearson’s correlation analysis, $P=0.33$) (Figure 2D). In all cases of available follow-up MRI, CE FLAIR signal subsided to undetectable along with the resolution of vasospasm. A multivariate analysis exploring the association of demographic factors and neurological score components with the severity of CE FLAIR signal revealed only positive correlation with PRES like edema (effect estimate, 3.922; 95% confidence interval, 0.29 to 0.753; $P=0.037$) suggesting an overall more benign clinical course in our cohort in comparison to previous reports.5,6

We suggest that contrasted enhancement on FLAIR imaging may reflect an early vasogenic process7,8 of either delayed blood flow or local BBB disruption with a capillary leak as proposed recently in an earlier mentioned cohort9 and in a later very compelling study, also of Asian population.6 The earlier studies showed a correlation between leptomeningeal gadolinium enhancement on FLAIR imaging and neurological outcome, leading to diagnostic changes in unclear cases. While these studies were performed in an Asian population, our cohort was comprised of exclusively Jewish women, which provides a further validation of the findings.

In two most devastating cases, initial computed tomography angiography was normal or not performed, delaying correct diagnosis and appropriate treatment. A lack of correlation between CE FLAIR signal and degree of vasospasm supports a more complex role of putative vascular dysregulation in parenchymal involvement of RCVS.

We believe that this data represents an interesting radiological phenomenon in early RCVS that correlates to the clinical outcome of this rare but potentially devastating syndrome.

Supplementary materials

Supplementary materials related to this article can be found online at https://doi.org/10.5853/jos.2020.01004.

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Supplementary materials

Patients
Altogether 25 patients above the age of 18 with were initially surveyed in the study. We included patients that presented with suspected reversible cerebral vasospasm syndrome according to clinical course and initial imaging. The clinical inclusion criteria included headache with or without thunderclap component, with or without focal neurological signs at presentation combined with subsequent suggestive imaging (magnetic resonance [MR] angiography or computed tomography [CT] angiography). Patients without definite vasospasm on the imaging were excluded from the analysis (two patients), as well as patients without available MR imaging due to artificial implants (one patient). In addition, we excluded from the study patients with initial intracranial stenosis on presentation, which on follow-up was proven to be due to either severe atherosclerosis or vasculitis (two patients). The retrospective evaluation of patient files was approved by the ethical committee of the Chaim Sheba Medical Center (Helsinki committee approval number 6067-19). Clinical data was gathered and documented, including the incidence of brain ischemia and seizure episodes.

Imaging
All our patients underwent brain CT angiography and transcranial ultrasound Doppler imaging. In several patients, conventional digital subtraction angiography (DSA) was also performed at presentation and follow-up.

In most cases MR imaging, including MR angiography, was performed during the first few days of presentation. In some cases, the MR scan preceded the established diagnosis of cerebral vasospasm on angiography. Most of the patients underwent a follow-up magnetic resonance imaging (MRI) scan. All the clinical data is summarized in Supplementary Table 1.

CT imaging was performed on either a General Electric Revolution 256 scanner or a Philips ICT256 station. Injected contrast media was based on iohexol solution (Omnipaque 350 mg I/mL) by General Electric Healthcare (Chicago, IL, USA). DSA was performed by experienced interventional neuroradiologists, on a biplane Siemens Artis (Munich, Germany) angiography system, utilizing the same iohexol based solution mentioned above.

MRI imaging was acquired on a Philips™ Ingenia 3.0 Tesla scanner, injected contrast media included gadoteric acid solution (Dotarem, at a concentration of 9.1 g/100 mL).

Image processing
The diagnosis of cerebral vasospasm on CT angiography was established via consensus of a neuroradiologist and an interventional neurologist. Two vascular neurologists confirmed cerebral vasospasm on transcranial Doppler imaging. MR imaging was reviewed independently by two neuroradiologists and an interventional neurologist. The degree of cerebral vasospasm was determined by quantifying the number of affected vessels (middle cerebral artery, anterior cerebral artery, posterior cerebral artery, superior cerebellar artery, basilar artery, anterior inferior cerebellar artery, posterior inferior cerebellar artery) and also by transcranial Doppler velocities measurements of the affected vessels on presentation and follow-up.

We graded the severity of reversible cerebral vasospasm syndrome (RCVS) by a composite neurological score that included posterior reversible encephalopathy syndrome (PRES) like edema appearance on MRI (0, 1), clinical seizures (0, 1), subarachnoid hemorrhage (0, 1), brain ischemia (0, 1) and thunderclap headache on initial presentation (0, 1). Multivariate logistic regression analysis was used to assure that the score components were not affected by demographic or clinical variables. The score was devised according to previously described markers of RCVS severity. The grading of contrast enhanced fluid attenuation inversion recovery (CE FLAIR) included the composite of intensity of sulci enhancement by contrast (0, no signal; 1, for mild signal; 2, for substantial signal) with its distribution throughout the brain (1 point for each involved lobe—including cerebellar hemispheres; 0–10).

Inter-rater agreement was excellent on every radiological evaluation (MRI, MR angiography, CT angiography, DSA, transcranial Doppler imaging).

Laboratory studies
All the patients underwent basic and advanced laboratory studies based on routinely accepted studies at the Sheba Medical Center Laboratory Division, including ruling out of rheumatologic and hypercoagulable conditions. Most of the patients also underwent a lumbar puncture to exclude subarachnoid bleed as a possible trigger and/or active inflammation to rule out vasculitic pathology.

Statistical analysis
Pearson correlation coefficient was calculated to establish various effects on either composite neurological outcome or CE FLAIR scoring. Multivariate analysis was performed as well in order to rule out mixed effects on the scores. Cutoff for statistical significance was set up at P<0.05. The analyses were performed using Excel Statistical functions (Microsoft Corporation, Redmond, WA, USA) and GraphPad Prism software (San Diego, CA, USA).
**Supplementary Table 1. Summary of individual patients characteristics**

| No. | Age | Sex | Prior medical history | Concurrent medications | DEFINITE RCVS | Vessels involved on CTA, MRA, or angiography and reversal on follow-up | PRES extent | Max velocity on TCCD (m/sec) | CE FLAIR enhancement score | MRI timing (day from neurological signs onset) | CSF protein (mg/dl) | CSF cell count (cells/mL) | Thunderclap headache | Clinical seizure | SAH | Stroke | Com-posite Severity score | RCVS causes | MRI follow-up | CE FLAIR resolution |
|-----|-----|-----|------------------------|------------------------|----------------|-------------------------------------------------|-------------|----------------------------|----------------------------|---------------------------------|----------------|---------------------------|----------------------|----------------|-----|--------|-------------------|--------------|----------------|---------------------|
| 1   | 36  | F   | Non-significant        | +                      | Bil MCA, AOA, LPCA, BA, bil SOA | 0 | 261 | 6 | 0 | 32 | 0 | + | – | – | + | 2 | Drugs or sub-stances | NA |
| 2   | 52  | F   | Non-significant        | +                      | RMCA, RPCA, RACA, LMCA | 2 | 123 | 8 | 1 | 46 | 0 | – | + | + | – | 3 | Drugs or sub-stances | Yes |
| 3   | 40  | F   | APLA, FMF              | +                      | Bil MCA, AOA, PCA | 2 | 101 | 6 | 3 | 44 | 2 | – | – | – | – | 1 | Idiopathic | NA |
| 4   | 26  | F   | Non-significant        | +                      | LMCA, bil PCA | 0 | 115 | 2 | 1 | 22 | 0 | – | + | – | – | 1 | Drugs or sub-stances | NA |
| 5   | 63  | F   | s/p bil mastectomy, remission, HTN | +                      | Bil ACA, LMCA | 0 | 125 | 9 | 1 | 40 | 2 | + | – | + | – | 2 | Idiopathic | NA |
| 6   | 41  | F   | Non-significant        | +                      | Mild bil MCA | 0 | 228 | 1 | 2 | 96 | 0 | – | – | – | – | 0 | Pregnancy or post-partum | NR |
| 7   | 48  | F   | Non-significant        | +                      | Bil ACA, RMCA | 0 | NA | 0 | 2 | 36 | 0 | + | – | – | – | 1 | Other medical condition | NR |
| 8   | 26  | F   | RF in childhood, migraines | –                      | None | 0 | NA | NR | 30 | 29 | 0 | – | – | – | – | NR | Drugs or sub-stances | NR |
| 9   | 48  | F   | Non-significant prior, new APS diagnosis | +                      | RACA, RMCA, RPCA | 0 | 285 | 5 | 12 | 53 | 6 | – | – | – | + | 1 | Drugs or sub-stances | Partial |
| 10  | 62  | F   | IHD, HTN, cardiac pacemaker, s/p bil supraclinoid aneurysm coiling | +                      | Bil ACA, PCA, MCA | NA | NR | NA | NA | 150 | 0 | + | + | + | – | NR | Idiopathic | NA |
| 11  | 42  | F   | Non-significant        | +                      | RMCA, RACA | 0 | NA | 6 | –2 | Normal | 0 | – | + | + | + | 3 | Idiopathic | Yes |
### Supplementary Table 1. Continued

| No. | Age | Sex | Prior medical history | Concurrent medications | DEFINITE RCVS on CTA, MRA, or angiography and reversal on follow-up | Vessels involved on CTA, MRA, or angiography | PRES extent | Max velocity on TCCD (m/sec) | CE FLAIR enhancement score | MRI timing (day from neurological signs onset) | CSF protein (mg/dl) | CSF cell count (cells/mL) | Thunderclap headache | Clinical seizure | SAH | Stroke | Com­posite Severity score | RCVS causes | MRI follow-up CE FLAIR resolution |
|-----|-----|-----|-----------------------|------------------------|------------------------------------------------------------------|-----------------------------------------------|------------|----------------------------|--------------------------------|--------------------------------|-----------------|--------------------------|--------------------|------------------|-----|--------|--------------------------|-------------|-------------------------------|
| 12  | 23  | F   | F2 heterozygote, DVT and recurrent abortions | Clexane during pregnancies | + Bil ACA, MCA, SCA | 0 | 154 | 8 | −2 | 57 | 5 | + | + | − | + | 3 | Pregnancy or post-partum | Yes |
| 13  | 22  | F   | Migraines | None | − None | NR | 157 | NR | 1 | NA | NA | + | − | − | − | 1 | Idiopathic | NA |
| 14  | 27  | F   | Non-significant | None | + Bil distal MCA | 1 | 169 | 1 | 0 | NA | NA | − | + | − | − | 2 | Pregnancy or post-partum | Yes |
| 15  | 26  | F   | Migraines | None | + Bil MCA, BA | 2 | 166 | 8 | 1 | NA | NA | + | − | − | − | 2 | Pregnancy or post-partum | Yes |
| 16  | 60  | F   | Stroke, IHD | Aspirin, plavix | − LMCA, bil PCA | NR | 70 | NR | 1 | 65 | 0 | + | − | + | − | NR | Idiopathic | Yes |
| 17  | 42  | F   | Non-significant | None | − Bil ACA | NR | 91 | NR | 2 | NA | NA | + | − | − | − | NR | Pregnancy or post-partum | No |
| 18  | 59  | F   | Non-significant | None | + LACA, LMCA, LSCA | 0 | 223 | 6 | 1 | 34 | 0 | + | − | − | − | 1 | Drugs or substances | Yes |
| 19  | 58  | F   | Non-significant | None | + RPCA, bil ACA, bil MCA | 0 | 87 | 8 | −5 | 31 | 0 | + | − | + | − | 2 | Idiopathic | Yes |
| 20  | 35  | F   | DM, aplastic anemia | Prednisone 40 mg, fluconazole, cyclosporine 175 mg bid, lantus | + Bil MCA, ACA, PCA, SCA, BA | 0 | 245 | 3 | −2 | NA | − | − | − | + | 1 | Drugs or substances | Yes |
| No. | Age | Sex | Prior medical history | Concurrent medications | DEFINITE RCVS (on CTA, MRA, or angiography and reversal on follow-up) | Vessels involved on CTA, MRA, or angiography | PRES extent | Max velocity on TCCD (m/sec) | CE FLAIR enhancement score | MRI timing (day from neurological signs onset) | CSF protein (mg/dL) | CSF cell count (cells/mL) | Thund erclap headache | Clinical seizure | SAH | Stroke | Composite Severity score | RCVS causes | MRI follow-up CE FLAIR resolution |
|-----|-----|-----|-----------------------|------------------------|-------------------------------------------------|-----------------------------------------------|-------------|----------------------|--------------------------|-----------------------------------------------|-----------------|-------------------------|---------------------|-----------------|-----|--------|--------------------------|-------------|--------------------------|
| 21  | 39  | F   | Episodic migraine     | None                   | + Bil MCA, Bil VA, BA                            | 0                                             | 53          | 2                    | 3                        | −6                                                           | 44              | 0                       | −                   | −               | −   | −      | 0                        | Other medical condition | NA                       |
| 22  | 65  | F   | Breast malignancy metastatic | Chemotherapy           | + Bil ACA, Bil MCA                              | 0                                             | 122         | 3                    | 2                        | −5                                                           | 74              | 7                       | +                   | −               | −   | −      | 2                        | Other medical condition | Yes                      |
| 23  | 65  | F   | Dyslipidemia, hypertension | Eltrox, Losar dex      | + Bil MCA, Bil PCA                              | 0                                             | 194         | 3                    | 3                        | −5                                                           | 95              | 5                       | +                   | −               | −   | −      | 1                        | Idiopathic              | Yes                      |
| 24  | 35  | F   | Non-significant       | None                   | + Bil ACA, RMCA, BA                             | 1                                             | 132         | 6                    | 6                        | −11                                                          | NA              | NA                      | +                   | +               | −   | −      | 4                        | Drugs or sub-stances      | Yes                      |
| 25  | 33  | F   | Episodic migraine     | None                   | + Bil VA                                         | 0                                             | 50          | 0                    | 14                       | NA                                                          | NA              | NA                      | +                   | −               | −   | −      | 1                        | Drugs or sub-stances      | NR                       |

DEFINITE RCVS, reversible cerebral vasoconstriction syndrome; CTA, computed tomography angiography; MRA, magnetic resonance angiography; PRES, posterior reversible encephalopathy syndrome; TCCD, transcranial color Doppler imaging; CE FLAIR, contrast enhanced fluid attenuation inversion recovery; MRI, magnetic resonance imaging; CSF, cerebrospinal fluid analysis; SAH, subarachnoid hemorrhage; Bil, bilateral in regard to artery; MCA, middle cerebral artery; ACA, anterior cerebral artery; LPOA, left posterior cerebral artery; BA, basilar artery; SOA, superior cerebellar artery; NA, non-available; RMCA, right middle cerebral artery; RPCA, right posterior cerebral artery; RACA, right anterior cerebral artery; LMCA, left middle cerebral artery; APLA, antiphospholipid antibody; FMF, familial Mediterranean fever; PCA, posterior cerebral artery; s/p, status post; HTN, hypertension; NR, non-relevant; RF, rheumatic fever; APS, antiphospholipid syndrome; IHD, ischemic heart disease; DVT, deep vein thrombosis; LACA, left anterior cerebral artery; LSCA, left superior cerebellar artery; bid, twice a day; VA, vertebral artery.