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Case Report

Down syndrome associated moyamoya may worsen epilepsy control and can benefit from surgical revascularization☆

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ABSTRACT

Objectives: To examine outcome of bilateral extracranial to intracranial (EC-IC) bypass surgeries for a Down syndrome patient with hard-to-treat epilepsy and moyamoya.
Materials and methods: Superficial temporal arteries were anastamosed using an indirect bypass technique to middle cerebral arteries bilaterally to help limit perfusion deficits and seizure controls.
Results: Two superficial temporal to middle cerebral artery indirect bypass surgeries were performed within 3 months. Post-revascularization improvements included seizure control, gait, perfusion, wakefulness, language and quality of life.
Conclusion: In patients with Down syndrome and moyamoya, improvements in seizure control and quality of life may occur with EC-IC bypass procedures.
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1. Introduction

Down syndrome is associated with epilepsy and seizure burdens may worsen with age and progression of associated dementia [1,2]. Down syndrome may predispose to progressive intracranial vascular narrowing associated with moyamoya syndrome [3–9]. Moyamoya is a vascular syndrome of proximal internal carotid artery terminus narrowings and resultant poor perfusion and elevated stroke risk typically involving the anterior cerebral and middle cerebral artery territories [3–9]. Of patients with Down syndrome and moyamoya, approximately 26% may have epilepsy [10].

Perfusion abnormalities due to moyamoya may benefit from surgical revascularization with extracranial to intracranial artery bypass (EC-IC bypass), though outcomes mainly assess stroke-related compromises [10,11]. In this report we discuss the worsening of seizure controls due to moyamoya induced vascular narrowing and the betterment of both CNS perfusion and seizure control with bilateral surgical revascularization using EC-IC bypass.

2. Materials and methods

With informed parental consent, medical records were accessed and abstracted for data on seizure frequency, imaging, surgical interventions and both clinical and imaging outcomes. MRI Perfusion techniques were preformed according to RAPID software (Menlo Park, CA, USA) [12].

3. Case report

A 27-year-old female with Down syndrome, drug resistant epilepsy with recurrent focal impaired awareness seizures presented with worsening seizures. Imaging with both cerebral angiography and MRI demonstrated bilateral moyamoya disease (Figs. 1, 2), with classic flow compromise beginning at the terminus of bilateral internal carotid arteries. Over an 18 month period, serial MR perfusion studies utilizing Tmax (the time to maximum of the residue function) as a surrogate marker of cerebral hypoperfusion were obtained and showed increasing perfusion delays over the bilateral middle and anterior cerebral artery territories, concomitant with worsening seizure control (Fig. 2). Events could cluster and were exacerbated by presumptive orthostatic positional changes such as standing after prolonged sitting or toileting. On EEG a diffuse, poorly lateralized high voltage bifrontal pleomorphic delta was evident at baseline, though no falling events were captured on EEG. A multitude of anti-seizure medications were trialed and while they may have shown initial betterment of seizure controls,

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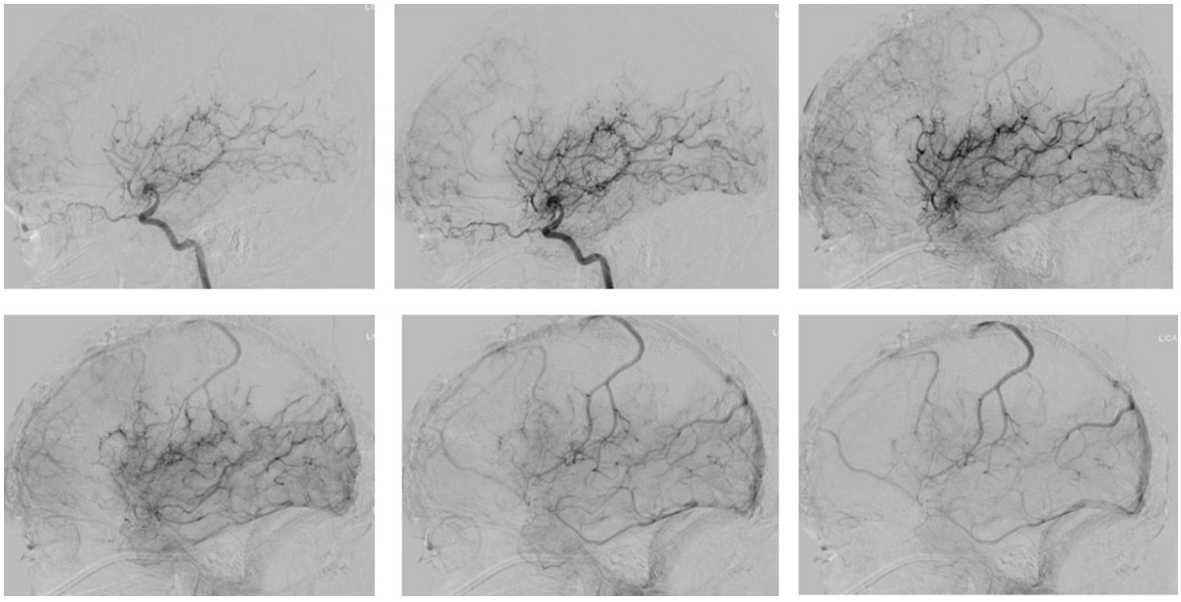

Fig. 1. Cerebral angiography with sequential preoperative lateral views of internal left internal carotid artery show narrowing beyond ICA terminus and minimal filling of what should be middle and anterior cerebral artery territories.

over the course of several years seizure control declined. Seizure types, medication burdens and time-based progression of findings, including seizure control are documented in the table. Her pre-operative exam was notable for classic phenotype of an ambulatory patient with Down syndrome in addition to minimal responsivity, progression towards expressive more than receptive aphasia and profound fatigue.

Because of increasing number of seizures and falls, and the known worsening in cerebral perfusion, she underwent a left indirect external carotid to internal carotid circulation bypass. Specifically the posterior auricular branch of the external carotid artery was sewn to the pial surface of the brain with dural eversion and temporal muscle placement on brain surface in an encephaloduromyosynangiosis (EDAMS) procedure. The more traditional donor of the superficial temporal artery was not utilized as it was already providing some collateral circulation to the brain. This was true of bilateral superficial temporal arteries. She recovered well and 3 months later returned for the same procedure on the

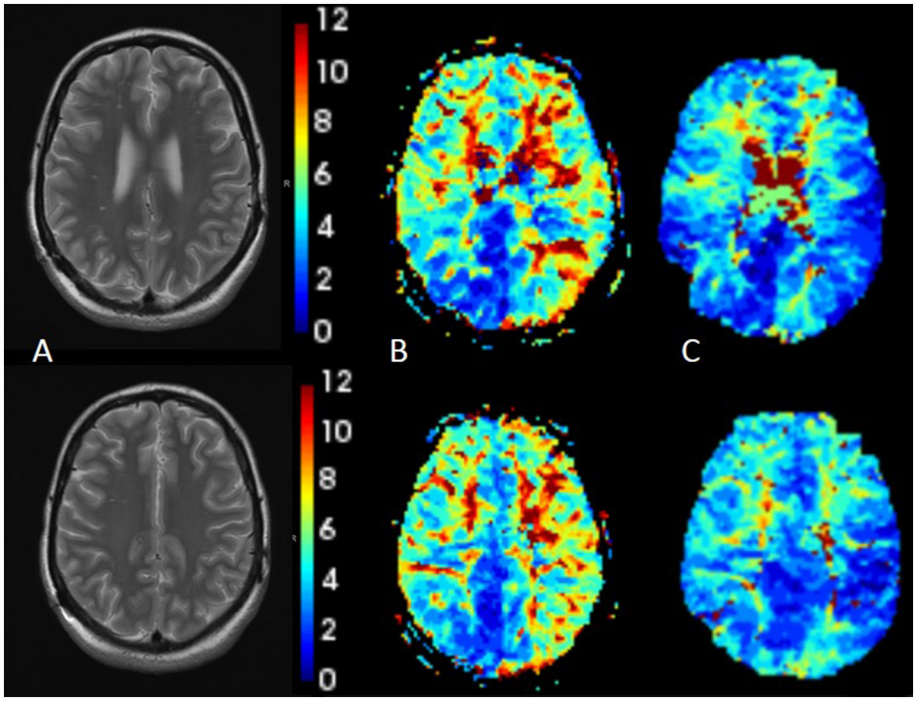

Fig. 2. Axial T2 MRI shows an absence of ischemic deficits (A). Representative images from parametric mapping of Tmax (transit time) perfusion imaging results before (B) and after (C) reperfusion, showing interval decrease in hypoperfused brain parenchyma. Automated quantification of perfusion imaging (RAPID) gives a reduction in tissue meeting threshold for hypoperfusion (Tmax > 6 s) from 150.7 cm^3 to 14 cm^3 (whole brain). Y-axis color units displayed are perfusion times in seconds. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 1
Clinical details.

Seizure type or clinical finding	10+ years prior to surgery	2 years prior to surgery	6 months prior to 1st surgery	1 year post both surgeries
Generalized onset tonic clonic	Two events	None	None	None
Generalized atonic	Once	None	None	None
Focal epilepsy manifest as focal impaired awareness with motor onsets (gasps, looks terrified, if progresses, elevates both arms and falls or slumps, shaking bilateral arms and legs)	1 per week	2–3 times a week	Daily	Very mild shaking may progress to fall and coincident with period or anticonvulsant medication reduction, less intense events, one every two months
Focal epilepsy manifest as non-motor onset behavior arrest, with emotional changes (cries) and cognitive changes (slowed responses)	Once	1–2 per month	1–2 per week	One event in 12 months
Language abilities:	Answered questions	Could not repeat	No words, no repetition	Greets people and uses her own name
MRI Perfusion studies	NA	No defect evident	Evident worsening, bilaterally in ICA territories	Improvements bilaterally, Fig. 2
Cognitive or other changes:	Won a ribbon for her horseback riding costume	Decreased energy, increasingly tired, was riding horses	Energy level and progressively more withdrawn and hypersomnolent, unable to ride horses	Increased energy, laughs frequently, better concentration, decreased need for sleep, blue ribbons for horseback riding in equitation (command following, rider posture, rider balance and rider's control of horse) and obstacle course success
Medications	Levetiracetam 2250 mg bid[a] Lamotrigine 250 mg bid[a]	Levetiracetam 2000 mg am 2500 mg pm Clobazam 20 mg bid Lamotrigine 300 mg am 200 mg pm Aspirin 81 mg	Levetiracetam 2000 mg am 2500 mg pm Clobazam 20 mg bid Lamotrigine 300 mg am 200 mg pm Aspirin 81 mg	Levetiracetam 1000 mg bid Clobazam 20 mg bid Lamotrigine 300 mg am 200 mg pm Aspirin 81 mg

[a] These two doses are from 5, not 10 years prior.

right side. Intraoperatively the posterior auricular branch was found to be extremely small, even for an onlay graft in continuity; and so only dural inversions and temporal muscle onlay grafts were performed.

Surgical outcomes post-operatively were excellent, At 15 months post-left bypass at one year post-right bypass there's been marked improvements while on triple drug anti-seizure medications (Table 1). She was more alert, showed a resolution of aphasia, used more spontaneous speech than she had in decades, no longer fell or slumped, and remained awake and alert during the day. Nine-month post-operative MRI scan shows marked improvements in bilateral CNS perfusion (Fig. 2).

4. Discussion

In Down syndrome patients with moyamoya we came across prior bypass attempts mainly using encephaloduroarteriosynangiosis [6]. The exact surgery involved is not described, though the outcome was a cessation of "further episodes." Cramer reported five patients with Down syndrome and moyamoya who were treated with bilateral pial synangiosis with no further strokes though no comment is made on seizure outcomes [9]. Cramer's series is probably included in a later case series of surgical outcomes with pial synangiosis which was performed in 49 of 51 surgeries from 32 children with Down syndrome and moyamoya, two in that series had direct EC-IC bypass [10]. From that same series clinical outcomes as measured by modified Rankin scores improved, one of 32 children had seizure control worsen postoperatively, epilepsy improvement outcomes pre- vs. post-surgery were otherwise not studied. Surgical complications were slightly higher in children with Down syndrome (5.9%) than in moyamoya patients without Down syndrome (4%) though long-term revascularization was better in patients with Down syndrome.

It has been postulated that chromosome 21 encodes a protein that may predispose to pathogenesis of moyamoya [9]. Furthermore, there may be amyloid precursor protein effects (housed on chromosome 21) that similarly predispose to progressive myoclonus epilepsy [2]. Given improvements in cognitive function postoperatively, we speculate the main reason for our patient's worsening of seizure control relates more to the progressive declines in cortical perfusion than amyloid deposition or dementia related changes.

5. Conclusion

Moyamoya should be assessed as an etiology for seizure controls worsening in patients with Downs syndrome. Importantly, EC-IC bypass procedures performed in a Down syndrome patient with moyamoya and hard-to-treat epilepsy had an outstanding outcome on seizure control, brain perfusion, cognition and quality of life. Based on this result, we suggest further study of epilepsy outcomes after revascularization procedures in patients with moyamoya, Down syndrome and epilepsy.

Conflict of interest

This paper has no financial support. Sarah Garson as well as Drs. Smith, Keogh, Monteith, Gwinn and Doherty have no disclosures.

Ethical statement

Informed consent was obtained for this case write up and the work has been carried out in accordance with The Code of Ethics of the World Medical Association.

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