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Refractory Vasospasm andArterial Ischemic Stroke in Meningoencephalitis: Novel Intrathecal Nitroprusside Treatment

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Keywords:

Vasospasm;Meningoencephalitis;Stroke;Intrathecal; Nitroprusside

Abbreviations:

AIS:AcuteIschemicStroke;BME:BacterialMeningoEncephalitis;CAV:CerebralArterialVasospasm;CSF:CerebralSpinalFluid;EVD:Extra-VentricularDrain;GCS:GlasgowComaScale;IA:Intra-Arterial;IT:Intra-Thecal;IV:Intravenous;MCA:MiddleCerebralArtery;MRA:MagneticRes- onance Angiography; MRI: Magnetic Resonance Imaging; SAH: Sub-Arachnoid Hemorrhage; TCD: Transcranial Doppler

1. Abstract

Background

Acutestrokeinbacterialmeningitisinchildrencontributestohigh morbidityandmortality.Theincidenceofstrokeinpediatricmeningitisisvaried,withreportsbetween8-42%,andassociatedmortality as high as 25%. The majority of these are arterial ischemic strokes(80-93%).Cerebralarterialvasospasmhasbeenproposed. We present the first case of intrathecal nitroprusside used to treat refractoryvasospasminachildwithbacterialmeningoencephalitis complicated by acute ischemic stroke.

Case Presentation

A7-year-old, vaccinated male with a past medical history of autism spectrum disorder and developmental delay was admitted to PICU with GCS of 3T, and CSF findings of streptococcal meningitis.SeveretranscranialdopplerandMRIrevealedvasospasm

in bilateral middle cerebral artery (MCA) and basilar artery, despite aggressive hemodynamic intervention, IV nimodipine, IV milrinone infusion. The patient was started on novel intra-thecal (IT) nitroprusside.After 4 doses, the patient's TCD markedly improved. A trial of discontinuing IT nitroprusside was attempted, however,wasabortedduetoneurologicalstatusdeteriorationand it was restarted. After 10 doses of IT nitroprusside, TCD values normalized and clinical improvement was observed, and the patient was eventually discharged.

Conclusion

This case highlights the use of IT vasodilator therapy in bacterial meningoencephalitis for refractory vasospasm with case-reproducibility and good outcome emphasizes the need for further studies and consensus guidelines on monitoring for vasospasm to prevent stroke in meningitis.

Background

Theincidenceofstrokeinbacterialmeningoencephalitis(BME)is 27-42%, with 80-93% being arterial ischemic stroke (AIS) and a 25% mortality rate in children [1-3]. Cerebral arterial vasospasm (CAV) is a proposed etiology for BME-associated AIS (BME-AIS),however,preventingBME-AIShasprovendifficultwithfirst line therapies [1-6].

Transcranialdoppler(TCD),establishedinsub-arachnoidhemorrhage (SAH) for detectingAIS, has emerging evidence for utility in BME [1-3]. In a study involving 94 adults with BME, TCD detectedBME-associatedCAV(BME-CAV)in41patients,which was associated with AIS and mortality [4 -9]. Additionally, in a studyinvolving20childrenwithBME,TCDaideddifferentiation of hyperemia, hypoperfusion, and vasospasm [10].

Initialevidence ofAIS prevention in BME-CAVsuggestseffective therapy may require a prolonged duration of action through permanent, repeated, or sustained contact of therapeutic agents and the arterial vessels involved.Although enteral and IVnimodipine haveprovenbeneficialinpatientswithSAH,thesewereofnoben- efit in the aforementioned trial involving 94 adults [11, 12]. Furthermore, small case series using intra-arterial (IA) percutaneous transluminalangioplastyandIAnicardipineandverapamiltotreat BME-CAV demonstrate promising results [13 - 15].

Insearchofalessinvasivetreatmentwithamoresustainedeffect, wepresentthefirstcaseofBME-CAVtreatedwithintrathecal(IT) nitroprusside.

2. Case Report

A7-year-old male with autism and developmental delay presented secondary to acute onset neurologic deficit with an admission Glasgow coma score (GCS) of 3T and cerebral spinal fluid suggesting streptococcal meningitis.

TCDonhospitalday2showedvasospasmoftherightmiddlecerebral artery (R-MCA) (Table 1). MRI revealed small, multifocal lenticulostriate AIS, ventriculitis and moderate hydrocephalus withunremarkableinitialMRangiography(MRA).Despiteexter- nal ventricular drain (EVD) insertion and systemic antibiotics, he continued to have only trace pain response, and status epilepticus developed on day 3.

Beginning day 6, serialTCDs and MRAs revealed bilateral MCA and basilar artery vasospasm refractory to enteral nimodipine and IV milrinone. Four-vessel angiogram on day 9 confirmed severe widespreadvasospasmandIAverapamilyieldednoimprovement.

Due to widespread severe vasospasm, evidence ofAIS, and continueddeteriorationdespiteallpriortreatments,ITnitroprusside4 mg every 12 hours via EVD was started on day 10. Nitroprusside was selected due to evidence of benefit in the adult literature for treatmentofCAVsecondarytoSAHandtheavailabilityofapreservative-freeformulation.TCDfindingsimprovedmarkedlyfollowingthefirstdosewithsustainedsuppressionofvasospasmand clinicalimprovementover4dosesthroughday12.Adiscontinuationtrialwasconductedandabortedwithin36hoursduetodeterioration inneurologicstatusandworseningvasospasmbyTCDand MRA(herein defined as case-reproducibility). Clinical status and vasospasm improved within 24 hours of reinitiating therapy. Ten totaldoseswereregivenwithsideeffectsconsistingofself-resolving hypertensive episodes and emesis.

Thereafter TCD values remained within normal limits and IT nitroprussidewasdiscontinuedonday17.Byday21thepatientwas extubated,milrinoneinfusionweanedoff,andtheEVDremoved. Atthattime,hehadimprovedencephalopathy(GCS11)andbrisk localizationtostimulation.Onday23hetransferredoutoftheICU followedby4weeksofinpatientrehabilitation.Duringafollow-up appointment four months after presentation, he was speaking in short phrases and walking unassisted (GCS 15) with no apparent extension of his original AISs clinically or by imaging.

Table1: SerialTranscranialDopplerResults.

Day of hospitalization	R-MCA Velocity(cm/s)	L-MCA Velocity(cm/s)	Lindegaard ratio Right/Left	Basilar a. Velocity(cm/s)	MRA	Anti-spasmodic therapy	Exam
2	198	167	4.2/2.4		No stenosis	None	coma
6	286	165	7.9/3.3	156		-Nimodipine 1 mg/kg q6	
7	162	196	5/4.6	148	narrowcaliber of the R+LMCAs	-Milrinone 0.5 mcg/kg/min -Nimodipine 1 mg/kg q6	coma
8	185	186	4.5/5.2	77		-Milrinone 0.75 mcg/kg/min	coma
9	218	168	5.7/3.7	x	narrowcaliber MCAs	-IAVerapamil -Milrinonegtt0.75 mcg/kg/min	coma
10	31	229	0.57/3.4	x	narrow caliber bilateralMCAs,	- ITNitroprusside 4 mg x1 -Milrinone 1 mcg/kg/min -Nimodipine 1 mg/kg q6	coma

11	183	134	3.5/2	100		- ITNitroprusside 4 mg x2 -Milrinone 1 mcg/kg/min -Nimodipine 1 mg/kg q6	coma
12	62	125	1.6/2.8	100		- ITNitroprusside 4 mg x1 -Milrinone 1 mcg/kg/min -Nimodipine 1 mg/kg q6	Open eyes
13	154	190	3.3/3.3	107		-*ITNitroprussideheld* -Milrinone 1 mcg/kg/min -Nimodipine 1 mg/kg q6	Coma
14	200	175	4.4/4.7	89	intervalincreased narrowing	- ITNitroprusside 4 mg x1 -Milrinone 1 mcg/kg/min -Nimodipine 1 mg/kg q6	Coma
15	103	138	2.5/2.8	x		- ITNitroprusside 4 mg x2 -Milrinone 1 mcg/kg/min -Nimodipine 1 mg/kg q6	Open eyes
16	211	69	4.1/2.1	144		- ITNitroprusside 4 mg x2 -Milrinone 1 mcg/kg/min -Nimodipine 1 mg/kg q6	Open eyes
17	213	153	3.9/2.6	x		- ITNitroprusside 4 mg x1 -Milrinone 1 mcg/kg/min -Nimodipine 1 mg/kg q6	Brisk localizing
20	113	140	1.66/2.86	65		-Milrinone 1 mcg/kg/min -Nimodipine 1 mg/kg q6	Brisk localizing
21	98	124	2.3/2.9	54		-Nimodipine 1 mg/kg q6	Brisk localizing

Lindegaardratioswereinterpreted asindicating vasospasmif equalto orgreater than 3.

a= artery; Day = day in reference to admission to intensive care unit; IT= intrathecal; L-MCAleft middle cerebral artery; MRA=magnetic resonance angiography; R-MCAright middle cerebral artery; x= not visualized or not reported.

(IT nitroprussidewaspreparedasfollows:1mLofnitroprusside25mg/mLin11.5mLofpreservative-free0.9%NaCltomakeafinalconcentration of 2 mg/mL).

3. Discussion

Toourknowledge,thisisthefirstreportofITvasodilatorfortreatmentofBME-CAV.Theauthorswereinitiallyconcernedthelack ofimprovementwithIVandIAvasodilatorsindicatedafixedanatomicalnarrowingofvesselsfromarteritisversustruevasospasm. Despitethis,therisk-benefitratiofavoredtreatmentastheimaging wasmoreconsistentwithvasospasm(smoothregularnarrowingof arterial walls). Confirming this hypothesis, arterial velocities and clinical exam improved quickly after IT nitroprusside initiation, worsened after treatment discontinuation, and again quickly improved with re-initiation.

Ultimately, the etiology of AIS in BME is unknown. Causative factors include anatomical obstructions from thrombi, vasculitis, andvasospasmthatcauseincreasedbloodflowvelocitiesbuthave different appearance on imaging [1-4].

ThepathophysiologyofBME-CAVispoorlyunderstoodandmay be caused by decreased nitric oxide secondary to bacterial consumption [5, 6]. The authors hypothesize nitroprusside, a nitric oxide donor, was effective for this child's refractory vasospasm duetoincreasedcontacttimebetweenthedrugandmajorcerebral arteries secondary to the IT route of administration.

Treatmentdurationofactionisimportantinvasospasmfromany

causeasIA-basedinterventionsoftenrequireserialadministration tomaintaineffectivenessandcarryknowncomplicationsofstroke, hemorrhage, permanent morbidity, and mortality. In comparison, IT vasodilators are not known to cause stroke, hemorrhage, permanentdisability,ormortality,andmayhaveequivalentorlonger durationofactioninBME,suggestedtobebetween24to48hours by this case.

AlthoughITnitroprussideisestablishedforvasospasmsecondary to SAH in adults, the timing of therapy initiation, dose, and delivery modality (continuous vs intermittent) is variable [7-9]. We began IT nitroprusside after failure of maximal therapy with enteralnimodipine,IVmilrinoneinfusion,andIAverapamil.Asthis was a novel approach in meningitis, a conservative dose frequen- cy of every 12 hours was used. This compares to published SAH protocols in which frequencies of every 5 minutes or continuous ITinfusionsarereported.[7-9]Furtherstudiesareneededtoestablish safety, efficacy, and optimal regimen.

TCD in this patient was a valuable, non-invasive tool for monitoring vasospasm and guiding therapy. TCD in BME has shown utility in predicting poor outcomes which may be related to vasospasmamenabletointervention.[10-11]Morestudiesontheutilityof TCD in pediatric BME are needed, which may prevent morbidity and mortality in children.

4. Conclusion

This sentinel case report of ITantispasmodic therapy in BME for refractoryvasospasmwithcase-reproducibilityandgoodoutcome highlightstheneedforfurtherstudies.Escalationofanti-spasmodictherapyinBMEtoITnitroprussidemaybeconsideredinthose withrefractoryvasospasmorwithcontraindications,orlackofaccess, to IA treatment when indicated.

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