Effects of acetazolamide in children with meningitis with increased intracranial pressure: a retrospective cohort study

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Accepted: January 2018
Latest revision: July 2018
Printed: October 2018

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ABSTRACT

OBJECTIVE

To investigate the effects of acetazolamide to reduce cerebrospinal fluid (CSF) pressure in children with meningitis and increased intracranial pressure.

METHODS

We conducted a retrospective cohort study of children (3 to 15 years old) with meningitis and increased intracranial pressure receiving acetazolamide and standard therapy and the children who received standard therapy alone in Khon Kaen Hospital, Thailand between Jan 2009 and December 2015. The primary outcome was the difference of opening CSF pressure change between these two groups.

RESULTS

A total of 85 patients were included in the analysis, 15 were prescribed acetazolamide and 70 were received standard treatment alone. The mean change of opening CSF pressure was similar between the two groups (-13.2±10.9 in acetazolamide group and -7.2±9.7 in the standard treatment group; mean difference, 6.05; 95% confidence interval (CI), -4.83 to 16.93; P=0.26). After adjusting the confounder, adjunct acetazolamide to standard treatment was not related to the opening CSF pressure change (regression coefficients [B], 1.15; 95% CI, -23.20 to 25.50), and the adverse effects included hypokalemia (adjusted odds ratio [AOR], 0.47; 95% CI, 0.06 to 4.06) and metabolic acidosis (AOR, 0.57; 95% CI, 0.07 to 4.76). However, opening CSF pressure at admission was inversely associated with the opening CSF pressure change (B, -0.66; 95% CI, -1.31 to -0.003).

CONCLUSION

In children with meningitis and increased intracranial pressure, adjunct acetazolamide to standard treatment did not have benefit in reduction of CSF pressure.

INTRODUCTION

Meningitis is a meningeal inflammation and is defined by an increased in a number of leukocytes in the cerebrospinal fluid (CSF), and is manifested by fever, generalized headache, nuchal rigidity, and alteration of consciousness.[1] Meningitis can be caused by bacteria, viruses, fungi, physical injury, cancer, systemic illness or certain drugs.[2,3] Meningitis can lead to increased intracranial pressure.[4] CSF pressure is measured by lumbar puncture (LP), normally ≤150 mmH_2O and considers the upper limit of normal CSF pressure to 200 mmH_20.[5-7] CSF is produced by choroid plexus in the ventricles and circulates through the subarachnoid space.[8,9] From an experiment in white rabbits in 1974, it showed that acetazolamide, a carbonic anhydrase inhibitor, decreased CSF production and resulted in a decrease in intracranial pressure.[10] Similarly, the studies in 1966 and 2012, suggested that acetazolamide is the main medical treatment for idiopathic intracranial hypertension.[11-13] From our extensive search, there are a few studies regarding the usage of acetazolamide in addition to standard treatment in patients with meningitis and increased intracranial pressure; a case series in Thailand published in 1979 suggested that repeated LP in 24 children patients with tuberculous meningitis and communicating hydrocephalus and adjunct treatment with acetazolamide could reduce the CSF pressure.[14] Later in 2002, there was an RCT comparing CSF pressure between those using adjunct acetazolamide to standard treatment and those with standard treatment alone in 22 Thai adults with cryptococcal meningitis and elevated intracranial pressure, however, the trial was terminated as patients who were prescribed acetazolamide developed severe metabolic acidosis and hyperchloremia.[15] In 2005, another randomized single-blinded pilot study in 18 adults with AIDS and cryptococcal meningitis and increased intracranial pressure in Uganda had demonstrated that acetazolamide combining with serial LP had no adverse effects and clinical improvement was observed.[16] These studies are mostly in adults with small sample size. Moreover, their conclusions were still controversial and were based on non-RCT studies. In the settings of Thailand, acetazolamide is still prescribed in some children with meningitis and increased intracranial pressure by expert opinions. Regarding reasons given above, our study aims to evaluate the effects of acetazolamide in a reduction of CSF pressure in children with meningitis and increased intracranial pressure.

METHODS

STUDY DESIGN

We conducted a retrospective cohort study to compare the effects of acetazolamide in a reduction of CSF pressure in children with meningitis and increased intracranial pressure admitted at Khon Kaen Hospital, Thailand from January 2009 to December 2015.

PATIENTS AND MEDICAL RECORD

We reviewed medical records of pediatric patients age 3 to 15 years old with diagnosis of any types of

Table 1. Characteristics of the patients

Characteristic	Standard treatment with acetazolamide (n=15)	Standard treatment (n=70)	P Value
Age – yr.	9.5±2.9	8.7±3.3	0.42
Male – no. (%)	11 (73.3)	50 (71.4)	>0.99
Findings on admission – no. (%)			
Headache	11 (73.3)	59 (84.3)	0.45
Fever	9 (60.0)	58 (82.9)	0.08
Neck stiffness	9 (60.0)	51 (72.9)	0.36
Cranial nerve palsy	1 (6.7)	6 (8.6)	>0.99
Hemiparesis	1 (6.7)	9 (12.9)	0.68
Seizure	5 (33.3)	15 (21.4)	0.33
Weight – kg			0.52
Median	26.0	20.5	
IQR	15.0-38.0	16.0-31.3	
Respiratory rate– breaths/min			0.84
Median	22	24	
IQR	22-28	22-24	
Blood pressure – mmHg			
Systolic			0.50
Median	113	110	
IQR	98-120	100-117	
Diastolic			0.03
Median	78	64	
IQR	60-80	60-70	
Score on Glasgow Coma Scale			0.74
Median	15	15	
IQR	14-15	14-15	
Score <8, indicating coma – no. (%)	1 (6.7)	4 (5.7)	>0.99
Peripheral-blood white-cell count–cell per mm3	n=15	n=65	0.78
Median	15,210	12,600	
IQR	6,900-17,600	8,765-19,250	
HIV infection– no. (%)	3 (20.0)	5 (7.1)	0.14
Serum electrolytes– mmol/liter			

Table 1. Characteristics of the patients

Characteristic	Standard treatment with acetazolamide (n=15)	Standard treatment (n=70)	P Value
Sodium	n=15	n=57	0.44
Median	135.0	135.0	
IQR	132.0-137.0	133.0-138.0	
Potassium	3.4±0.4	3.7±0.6	0.02
Chloride	n=15	n=53	0.87
Median	99.0	99.0	
IQR	93.0-104.0	95.0-102.5	
Bicarbonate	22.2±3.1	22.3±4.5	0.89
Serum creatinine – mg/dl	n=13	n=40	0.36
Median	0.5	0.5	
IQR	0.3-0.6	0.4-0.6	
Indexes of CSF inflammation			
Protein – mg/dl	n=15	n=56	0.92
Median	58.8	61.1	
IQR	41.6-143.2	40.5-116.8	
CSF sugar per blood sugar	0.4±0.2	0.5±0.2	0.009
White-cell count – cell per mm3	n=15	n=64	0.20
Median	358.0	53.5	
IQR	20.0-770.0	10.0-352.5	
CSF opening pressure at admission – cm of water	n=15	n=41	<0.001
Median	32.0	20.0	
IQR	27.0-48.0	16.0-26.5	
CSF closing pressure at admission – cm of water	n=15	n=37	0.12
Median	21.0	17.0	
IQR	16.0-26.0	13.6-21.0	
Pathogen from CSF profile or culture – no./total no. (%)			0.02
Bacteria	6/15 (40.0)	35/69 (50.7)	
Fungus	3/15 (20.0)	3/69 (4.3)	
Mycobacterium tuberculosis	4/15 (26.7)	6/69 (8.7)	
Other	2/15 (13.3)	25/69 (36.2)	

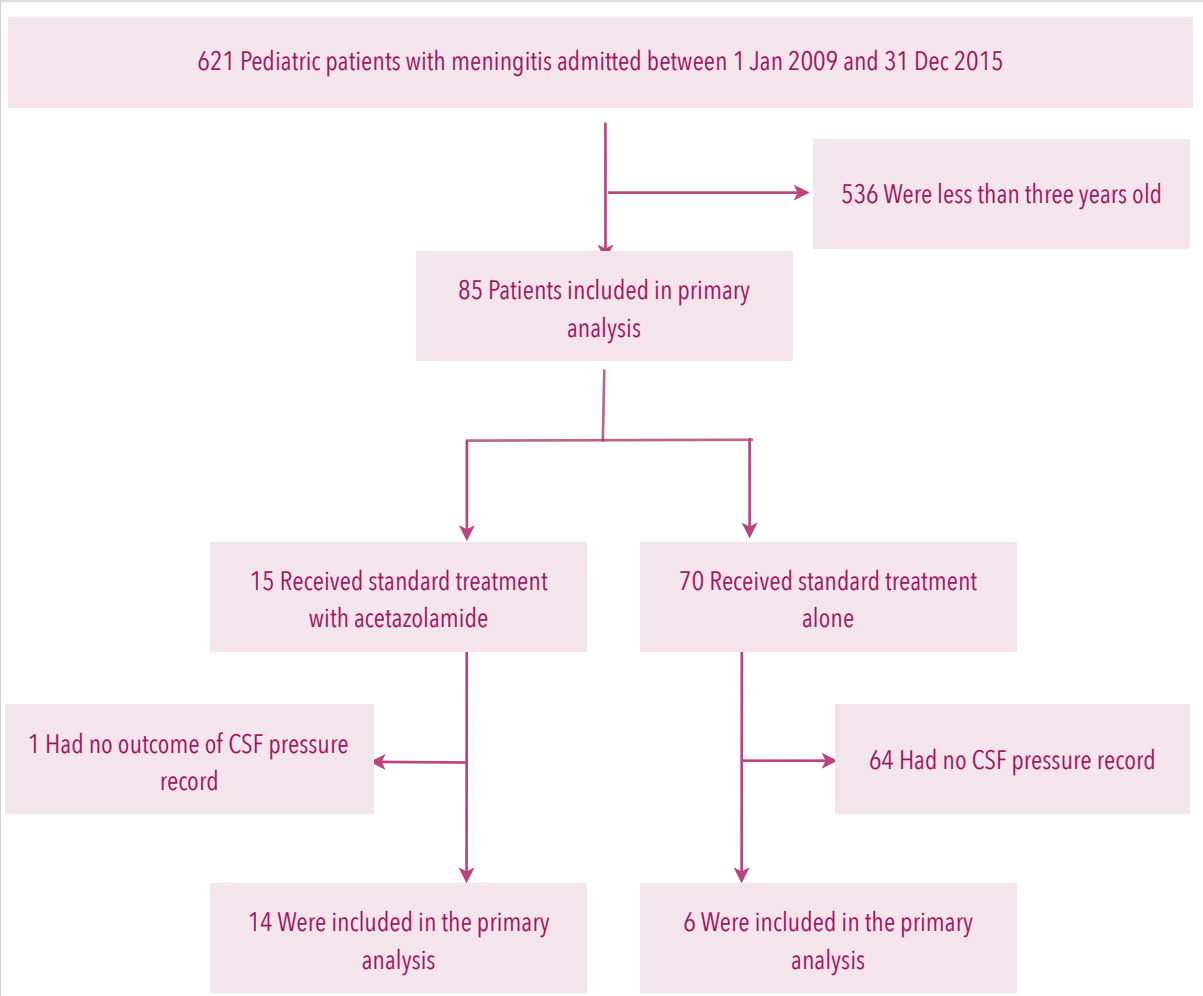

Figure 1. Study flow and assessment of primary outcomes

meningitis and increased intracranial pressure. We had no specific exclusion criteria.

DATA COLLECTION

All databases of patients diagnosed with meningitis using the International Classification of Disease (ICD) 10 and increased intracranial pressure who admitted at Khon Kaen Hospital.[17] For patients with readmission with the same diagnosis, every admission was included. The primary outcome in each patient was recorded into the mean of opening CSF pressure change between the admission date and the terminal date of treatment records. Furthermore, we recorded the characteristics such as age, sex, headache, fever,[18] neck stiffness, cranial nerve palsy, hemiparesis, seizure, weight, vital signs, score on Glasgow Coma Scale (GCS),[19] peripheral-blood white-cell count, HIV infection, serum sodium, serum potassium, serum chloride, serum

bicarbonate, serum creatinine, CSF values (protein, glucose, white-cell count, opening pressure, closing pressure), pathogen from CSF profile or culture.

OUTCOMES

The primary outcome was the difference of opening CSF pressure change before and after the treatment. The secondary outcomes were adverse drug effects included hypokalemia and metabolic acidosis.[22-25]

STATISTICAL ANALYSIS

We used descriptive statistics to summarize baseline characteristics of patients in each group; number and percent for categorical variables, mean with standard deviation (SD) for normally distributed continuous variables, and median and interquartile range (IQR) for non-normally distributed continuous variables. For inferential statistics, categorical variables were compared using the chi-square test; normally distributed continuous variables were compared using student t-test while the Mann-Whitney U test was used for comparing non-normally distributed continuous variables. For the difference of opening CSF pressure change between the two groups, we analyzed by using mean difference and we used linear regression to estimate B and corresponding 95% CIs for the risk factors associated with the outcome.[20,21] Relative risk was reported for the event rate of the secondary outcomes between the two groups and the adjusted odds ratio for the risk factors that associated were analyzed by logistic regression. We considered $P<0.05$ were significant difference.

RESULTS

CHARACTERISTICS OF THE PATIENTS

Initially, the medical records of 621 pediatric patients diagnosed with meningitis from KKH database were reviewed, 536 were excluded due to younger than 3 years old, 85 were met the inclusion criteria and included in this study, 15 were treated with acetazolamide and 70 were treated with standard treatment alone. After excluding 65 patients with no CSF pressure record, one was treated with acetazolamide group and 64 in standard treatment alone group, 20 were included in the analysis of the primary outcome (Figure 1). Their mean (±SD) age was 8.9±3.3 years old. Approximately 70% were male. There were few HIV-infected patients (9.4%). The median weight was 24 kg (IQR 16 to 34). Their median respiratory rate was 24 (IQR 22 to 24). Their median systolic blood pressure was 110 mmHg (IQR 100 to 118) and their mean diastolic blood pressure was 66 mmHg (IQR 60 to 73). Most of the patients had 15 scores in GCS (71.8%). The median peripheral-blood white-cell count was 13,350 cell/mm³ (IQR 8,732.5 to 18,875). Serum electrolytes and serum creatinine often were within normal range. The median CSF protein levels and white-cell counts were 61 mg/dl (IQR 41.6 to 119) and 62.5 cell/mm³ (IQR 10 to 430), respectively. The mean CSF sugar per blood sugar was 0.5±0.2. The median opening pressure and the mean close pressure were 22 cmH_2O (IQR 17.13 to 32) and 19.1±7.7 cmH_2O, respectively. As expected, most of the patients had a headache (82.4%), fever (78.8%), and neck stiffness (70.6%), but, few children had a seizure (23.5%),

Table 2. The primary and the secondary outcomes after treatment

Outcomes	N	Standard Treatment with acetazolamide	Standard treatment	Mean difference (95% CI)	Relative risk (95% CI)	P Value
Opening CSF pressure change*	20	-13.2±10.9	-7.2±9.7	6.05 (-4.83- 16.93)		0.26
Hypokalemia†	44	3 (23.1)	6 (19.4)		1.19 (0.35-4.06)	>0.99
Metabolic acidosis‡	31	7 (63.6)	12 (60)		1.06 (0.60-1.88)	>0.99

Plus–minus values are means ±SD.

*Opening CSF pressure change between the admission date and the terminal date of treatment records

†Serum potassium<3.5 mmol/L

‡Bicarbonate<22 mmol/L

hemiparesis (11.8%), and cranial nerve palsy (8.2%). Nearly half of them were bacterial meningitis.

The characteristics of those receiving acetazolamide and those not receiving acetazolamide were similar in relation to age, sex, weight, HIV infection, respiratory rate, systolic blood pressure, score on GCS, clinical findings on admission, peripheral white blood cell, serum sodium, serum chloride, serum bicarbonate, serum creatinine, CSF protein, white blood cell in CSF, CSF opening and closing pressure at admission (Table 1). However, the former group had higher diastolic blood pressure (P=0.03), lower serum potassium (P=0.02), lower CSF sugar per blood sugar (P=0.009), higher CSF opening pressure at admission (P<0.001), higher proportion of patients with fungus and Mycobacterium tuberculosis meningitis, and lower proportion of bacterial and other meningitis (P=0.02) (Table 1).

OUTCOMES

There was no difference in term of mean change of opening CSF pressure between the two groups (-13.2±10.9 in acetazolamide group and -7.2±9.7 in the standard treatment group; mean difference, 6.05; 95% CI, -4.83 to 16.93; P=0.26) (Table 2). Similarly, the secondary outcomes, there was no difference in hypokalemia between acetazolamide treatment group (23.1%) and standard treatment group (19.4%) (RR, 1.19; 95% CI, 0.35 to 4.06; P>0.99), and metabolic acidosis between acetazolamide treatment group (63.6%) and standard treatment group (60%) (RR, 1.06; 95% CI, 0.60 to 1.88; P>0.99) (Table 2).

FACTORS ASSOCIATED WITH THE OUTCOMES

From the linear regression and logistic regression analysis, acetazolamide was not associated with the opening CSF pressure change, hypokalemia, and metabolic acidosis (B, 1.15; 95% CI, -23.20 to 25.50; AOR, 0.47; 95% CI, 0.06 to 4.06; AOR,

Table 3. Risk factors associated with the outcomes

Factors	Opening CSF pressure change B coefficient (95% Confidence interval)	Hypokalemia Adjusted odds ratio (95% Confidence interval)	Metabolic acidosis Adjusted odds ratio (95% Confidence interval)
Age	-0.84 (-5.00 to 3.32)	0.61 (0.30 to 1.20)	0.89 (0.45 to 1.76)
Weight	0.14 (-0.82 to 1.10)	1.11 (0.96 to 1.27)	1.01 (0.88 to 1.16)
Acetazolamide treatment	1.15 (-23.20 to 25.50)	0.47 (0.06 to 4.06)	0.57 (0.07 to 4.76)
Serum potassium at admission	2.48 (-17.50 to 22.45)	0.18 (0.008 to 3.94)	0.62 (0.03 to 13.94)
Serum bicarbonate at admission	0.18 (-1.46 to 1.82)	0.99 (0.78 to 1.27)	0.95 (0.711 to 1.27)
Opening CSF pressure at admission	-0.66 (-1.31 to -0.003)	1.02 (0.94 to 1.10)	1.03 (0.94 to 1.12)

*The data show the regression coefficients.

0.57; 95% CI, 0.07 to 4.76, respectively) (Table 3). However, opening CSF pressure at admission was inversely associated with the opening CSF pressure change (B, -0.66; 95% CI, -1.31 to -0.003) (Table 3).

DISCUSSION

MAJOR FINDINGS

In our study, we found that acetazolamide was not associated with the opening CSF pressure change, hypokalemia, and metabolic acidosis. However, opening CSF pressure at admission was the only factor associated with the opening CSF pressure change.

STRENGTHS AND LIMITATIONS OF THE STUDY

Our study is the first retrospective cohort design, that did in children and any causes of infectious meningitis. However, several limitations of this study should also be mentioned, firstly the sample size that the study required was 100 patients, but, in fact, ours was 85 patients, it was slightly different. Secondly, the medical records were not complete as some cases had no records of CSF pressure especially the record before discharge because in the case of improved clinical symptoms, the physician would not repeat LP for measuring CSF pressure and the patient would reject the procedure for those reasons the CSF pressure change could not access and it also was the one reason why we excluded some cases. Thirdly, the interval in each LP was varied. In addition, the LP technique, the measurement technique and the experiences of practitioners have affected by the measure of the CSF pressure.

COMPARISON WITH PREVIOUS STUDIES

In our study, we found that adjunct acetazolamide to standard treatment in children with any causes

of infectious meningitis and increased intracranial pressure had no difference in reduction of CSF pressure and adverse effects to standard treatment alone similar to the previous randomized single-blinded pilot study, from Uganda in 2005, the result showed no adverse effects and reduction in intracranial opening pressure.[16] However, the study performed in only 18 adult patients with AIDS and cryptococcal meningitis and increased intracranial pressure, which the intervention also combined with serial LP and the primary outcome was focused on clinical improvement. Only one study that found the adverse effects of acetazolamide was an RCT in 2002, comparing CSF pressure between those using adjunct acetazolamide to standard treatment and those with standard treatment alone in 22 Thai patients, also studied in adults with cryptococcal meningitis and elevated intracranial pressure, was terminated as patients who were prescribed acetazolamide developed severe metabolic acidosis and hyperchloremia.[15] However, there was a case series of 24 children, in 1979, suggested that repeated LP combined with acetazolamide adjunct to standard treatment could reduce the CSF pressure.[14] But there was no comparison group and performed in only children patients with tuberculous meningitis and communicating hydrocephalus.

Acetazolamide, however, is used as the main medical treatment for idiopathic intracranial hypertension (IIH) for reduction of CSF production.[11,13] The evidence supports in this condition are the same as mentioned earlier and no studies can confirm the effectiveness of acetazolamide. Prior case series in children with IIH mentioned the success for improving symptoms of increased intracranial pressure and vision more than half patients.[26,27] Subsequently, the pilot RCT of 50 patients in the United Kingdom, 2010, is difficult to practice due to poor recruitment and compliance.[28] And their limitation is the same as ours in the term of sample size. Later, in 2014, a multi-center, double-blinded, RCT of 86 patients in the United States showed the improvement of visual field function but did not mention of other benefits.[29]

CONCLUSION AND IMPLICATION

Adjunct acetazolamide to standard treatment had no difference in reduction of CSF pressure in children with meningitis and increased intracranial pressure. However, for better estimation effects of acetazolamide, the larger sample size is needed. Multi-center retrospective cohort design should be conducted in settings where acetazolamide is of use for preliminary approximation effects of acetazolamide before conducting an RCT.

ACKNOWLEDGMENTS & DECLARATION

The authors would like to thank Dr. Thammasorn Jeeraaumponwat for his supervision, guidance, and all of his support to help us complete the present study. We also would like to thank Khon Kaen Medical Education Center for all resources offered to us and Department of Medical Information System, Khon Kaen Hospital for data accessing.

COMPETING INTERESTS: This study has no competing on interest.
FUNDING: None

REFERENCES

1. Clinical features and diagnosis of acute bacterial meningitis in adults [Internet]. [cited 2016 Mar 6]. Available from: http://www.uptodate.com/contents/clinical-features-and-diagnosis-of-acute-bacterial-meningitis-in-adults

2. Meningitis | Home | CDC [Internet]. [cited 2016 Mar 6]. Available from: http://www.cdc.gov/meningitis/index.html

3. Overview of meningitis - Introduction - Best Practice - English [Internet]. [cited 2016 Mar 6]. Available from: http://bestpractice.bmj.com/best-practice/monograph/111.html

4. Bacterial meningitis in children: Neurologic complications [Internet]. [cited 2016 Mar 6]. Available from: http://www.uptodate.com/contents/bacterial-meningitis-in-children-neurologic-complications?source=see_link&sectionName=INCREASED+INTRACRANIAL+PRESSURE&anchor=H6#H6

5. Lumbar puncture: Technique, indications, contraindications, and complications in adults [Internet]. [cited 2016 Mar 6]. Available from: http://www.uptodate.com/contents/lumbar-puncture-technique-indications-contraindications-and-complications-in-adults?source=search_result&search=Cerebrospinal+fluid+opening+pressure+change&selectedTitle=2%7E150

6. Medline ® Abstract for Reference 2 of "Cerebrospinal fluid: Physiology and utility of an examination in disease states" [Internet]. [cited 2016 Mar 7]. Available from: http://www.uptodate.com/contents/cerebrospinal-fluid-physiology-and-utility-of-an-examination-in-disease-states/abstract/2?utdPopup=true

7. Diagnosis and management of benign intracranial hypertension -- Soler et al. 78 (1): 89 -- Archives of Disease in Childhood [Internet]. [cited 2016 Mar 6]. Available from: http://adc.bmj.com/content/78/1/89.full

8. Cerebrospinal fluid: Physiology and utility of an examination in disease states [Internet]. [cited 2016 Mar 6]. Available from: http://www.uptodate.com/contents/cerebrospinal-fluid-physiology-and-utility-of-an-examination-in-disease-states

9. Sakka L, Coll G, Chazal J. Anatomy and physiology of cerebrospinal fluid. Eur Ann Otorhinolaryngol Head Neck Dis. 2011 Dec; 128(6):309–16.

10. The effect of acetazolamide and furosemide on cerebrospinal fluid production and choroid plexus carbonic anhydrase activity. - PubMed - NCBI [Internet]. [cited 2016 Mar 6]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/4207244

11. Update on the pathophysiology and management of idiopathic intracranial hypertension -- Biousse et al. 83 (5): 488 -- Journal of Neurology, Neurosurgery & Psychiatry [Internet]. [cited 2016 Mar 6]. Available from: http://jnnp.bmj.com/content/83/5/488.full

12. Idiopathic intracranial hypertension (pseudotumor cerebri): Prognosis and treatment [Internet]. [cited 2016 Mar 6]. Available from: http://www.uptodate.com/contents/idiopathic-intracranial-hypertension-pseudotumor-cerebri-prognosis-and-treatment

13. Rubin RC, Henderson ES, Ommaya AK, Walker MD, Rall DP. The Production of Cerebrospinal Fluid in Man and Its Modification by Acetazolamide. J Neurosurg. 1966 Oct 1;25(4):430–6.

14. Hydrocephalus in tuberculous meningitis in children: treatment with acetazolamide and repeated lumbar puncture. - PubMed - NCBI [Internet]. [cited 2016 Mar 6]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/480050

15. Newton PN, Thai LH, Tip NQ, Short JM, Chierakul W, Rajanuwong A, et al. A Randomized, Double-Blind, Placebo-Controlled Trial of Acetazolamide for the Treatment of Elevated Intracranial Pressure in Cryptococcal Meningitis. Clin Infect Dis. 2002 Sep 15;35(6):769–72.

16. Orem J, Tindyebwa L, Twinoweitu O, Mukasa B, Tomberland M, Mbidde EK. Feasibility study of serial lumbar puncture and acetazolamide combination in the management of elevated cerebrospinal fluid pressure in AIDS patients with cryptococcal meningitis in Uganda. Trop Doct. 2005 Jan; 35(1):19–21.

17. 2016 ICD-10-CM Diagnosis Code G01: Meningitis in bacterial diseases classified elsewhere [Internet]. [cited 2016 Mar 6]. Available from: http://www.icd10data.com/ICD10CM/Codes/G00-G99/G00-G09/G01-/G01

18. Fever in children [Internet]. [cited 2016 Mar 7]. Available from: http://www.uptodate.com/contents/fever-in-children-beyond-the-basics

19. de Gans J, van de Beek D. Dexamethasone in Adults with Bacterial Meningitis. N Engl J Med. 2002 Nov 14;347(20):1549–56.

20. M Brenner RJM. Rate of FEV1 change following lung volume reduction surgery. Chest. 1998;113(3):652–9.

21. Andersen GS, Girma T, Wells JCK, Kæstel P, Michaelsen KF, Friis H. Fat and Fat-Free Mass at Birth: Air Displacement Plethysmography Measurements on 350 Ethiopian Newborns. Pediatr Res. 2011 Nov; 70(5):501–6.

22. Kabadi U, Acknowledgements. Assessment of hypokalaemia [Internet]. [cited 2016 Mar 6]. Available from: http://bestpractice.bmj.com/best-practice/monograph/59/diagnosis/differential-diagnosis.html

23. Approach to the adult with metabolic acidosis [Internet]. [cited 2016 Mar 6]. Available from: http://www.uptodate.com/contents/approach-to-the-adult-with-metabolic-acidosis?source=search_result&search=metabolic+acidosis&selectedTitle=1%7E150

24. Hypokalemia in children [Internet]. [cited 2016 Mar 6]. Available from: http://www.uptodate.com/contents/hypokalemia-in-children?source=search_result&search=hypokalemia+in+children&selectedTitle=1%7E150

25. Hypokalaemia (Assessment of) - Diagnosis - Differential diagnosis - Best Practice - English [Internet]. [cited 2016 Mar 7]. Available from: http://bestpractice.bmj.com/best-practice/monograph/59/diagnosis/differential-diagnosis.html

26. Idiopathic Intracranial Hypertension in Children [Internet]. [cited 2016 Mar 11]. Available from: http://jcn.sagepub.com/content/15/7/453.short

27. Drugs used in childhood idiopathic or benign intracranial hypertension -- Matthews 93 (1): 19 -- ADC - Education and Practice [Internet]. [cited 2016 Mar 11]. Available from: http://ep.bmj.com/content/93/1/19.short

28. A randomised controlled trial of treatment for idiopathic intracranial hypertension - Springer [Internet]. [cited 2016 Mar 11]. Available from: http://link.springer.com/article/10.1007/s00415-010-5861-4

29. JAMA Network | JAMA | Effect of Acetazolamide on Visual Function in Patients With Idiopathic Intracranial Hypertension and Mild Visual Loss: The Idiopathic Intracranial Hypertension Treatment Trial [Internet]. [cited 2016 Mar 11]. Available from: http://jama.jamanetwork.com/article.aspx?articleid=1861803