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Unexpected Relationship Between Tympanometry and Mortality in Children With Nontraumatic Coma

AUTHORS: Samson Gwer, MBChB, MRCPCH, PhD,[a,b] Eddie Chengo, DCM, MSc,[c] Charles R.J.C. Newton, MBChB, FRCPCH, MD,[c,d,e] and Fenella J. Kirkham, MBBChir, FRCPCH, MD[e,f]

[a]Department of Medical Physiology, College of Health Sciences, Kenyatta University, Nairobi, Kenya; [b]Department of Clinical Research, Afya Research Africa, Nairobi, Kenya; [c]Centre for Geographic Medicine Research–Coast, Kenya Medical Research Institute–Wellcome Trust Research Programme, Kilifi, Kenya; [d]Department of Psychiatry, University of Oxford, Oxford, United Kingdom; [e]Neurosciences Unit, Institute of Child Health, University College London, London, United Kingdom; and [f]Department of Child Health, Southampton University Hospital, Southampton, United Kingdom

WHAT'S KNOWN ON THIS SUBJECT: Tympanometry provides a measure of middle ear function. There has been no description of the relationship between measurements of middle ear function in the absence of gross anatomic defects and clinical outcome among children with acute nontraumatic coma.

WHAT THIS STUDY ADDS: This study reveals an unexpected association between abnormal middle ear function and death in childhood acute coma. These findings call for more investigations on the relationship between middle and inner ear anatomy and function and intracranial dynamics and clinical outcomes.

abstract

OBJECTIVE: We sought to further examine the relationship between tympanometry and mortality after noting an unexpected association on assessment of baseline data of a study whose primary aim was to investigate the utility of noninvasive tympanic membrane displacement measurement for monitoring intracranial pressure in childhood coma.

METHODS: We recruited children who presented with acute nontraumatic coma to the high-dependency unit of Kilifi District Hospital on the rural coast of Kenya. We excluded children with sickle cell disease, epilepsy, and neurodevelopmental delay. We performed tympanometry on the right ear before tympanic membrane displacement analyzer measurements. All children were managed according to standard World Health Organization guidelines.

RESULTS: We recruited 72 children with a median age of 3.2 years (interquartile range [IQR]: 2.0–4.3 years); 31 (43%) were female. Thirty-eight (53%) had cerebral malaria, 8 (11%) acute bacterial meningitis, 4 (6%) sepsis, and 22 (30%) encephalopathy of unknown etiology. Twenty (28%) children died. Tympanometry was normal in 25 (35%) children. Adjusting for diagnosis and clinical features of increased intracranial pressure, both associated with death on univariable analysis, children with abnormal tympanometry had greater odds of dying than did those with normal tympanometry (adjusted odds ratio: 17.0; 95% confidence interval: 1.9–152.4; P = .01). Children who died had a lower compliance (0.29 mL; IQR: 0.09–0.33 mL) compared with those who survived (0.48 mL; IQR: 0.29–0.70 mL) (P < .01).

CONCLUSIONS: Abnormal tympanometry appears to be significantly associated with death in children with acute nontraumatic coma. This finding needs to be explored further through a prospective study that incorporates imaging and intensive physiologic monitoring. *Pediatrics* 2013;132:e713–e717

Coma is a common complication of childhood illness in Africa,[1–3] most often caused by infections and associated with poor outcome, with up to 33% mortality and significant occurrence of neurocognitive sequelae among survivors.[1,2,4,5] Risk factors for poor outcome include recurrent seizures, shock, and increased intracranial pressure (ICP), clinical factors that are important targets for interventions.[2,5–7] However, increased ICP presents a challenge in management because monitoring requires invasive tools and expertise that are commonly lacking in most health facilities in Africa.[8] Noninvasive tools for detection of clinically important increased ICP may help alleviate this problem. Thus, we have been interested in exploring the utility of tympanic membrane displacement (TMD) as a tool for noninvasive ICP monitoring.[9] The reliability of TMD analyzer measurements is dependent on normal middle ear function, which can be assessed by tympanometry.

Tympanometry provides useful quantitative information on middle ear function, indicating presence of fluid in the middle ear, mobility of the middle ear system, and ear canal volume. Tympanogram tracings may be classified as normal (type A tracing) or abnormal (types B and C) by using criteria set out by Liden and Jerger.[10] This classification is based on a plot of the compliance of the tympanic membrane and middle ear pressure. Type B tracings are flat and indicate decreased mobility of the tympanic membrane, most commonly due to middle ear fluid or stiffness of the tympanic membrane from scarring. Other causes may include tympanosclerosis, cholesteatoma, and middle ear tumor. Type C tracings demonstrate a highly negative pressure in the middle ear correlating with a retracted tympanic membrane. Type C curves may be seen in upper respiratory tract infections in which the ventilatory function of the eustachian tube is impaired. Many studies recognize type B curve as definitely abnormal, whereas a type C curve is considered imprecise in determining middle ear abnormality when not correlated with other findings.[10]

In this brief report, we present our findings on the relationship between tympanometry and mortality among children with acute nontraumatic encephalopathy in a study whose primary objective was to explore the utility of the TMD analyzer for monitoring ICP.[9]

METHODS

Between November 2007 and September 2009, we performed tympanometry and TMD analyzer measurements and made clinical observations on children aged between 6 months and 13 years who presented with coma (Blantyre coma score [BCS] ≤2 indicating inability to localize painful stimuli and persisting for >30 minutes after correction of hypoglycemia or treatment of a seizure) to Kilifi District Hospital on the rural coast of Kenya.[9] The BCS is a simple score of coma status based on assessment of motor, verbal, and eye-opening ability, similar to the modified Glasgow and Adelaide coma scales but preferred in Africa because of its simplicity, specificity, and better interobserver agreement among health workers in this setting (Table 1).[11,12] After initial assessment at admission, the BCS was assessed every 4 hours by the attending clinicians. Study observations were stopped when the child was found to have a BCS >2. We excluded children known to have sickle cell disease, epilepsy, or developmental delay, as assessed through clinical history. The decision to replace this group of children was in consideration of the possibility of altered ICP dynamics in association with these conditions, and the likely difficulty in ruling out the role of these comorbid conditions in encephalopathic disease course and in determining new neurologic sequelae

TABLE 1 Blantyre Coma Score

Coma Score Parameter	Score
Best motor response	
Localizes painful stimulus	2
Withdraws limb from painful stimulus	1
No response or inappropriate response	0
Best verbal response	
Cries appropriately with pain or, if verbal, speaks	2
Moans or cries abnormally with pain	1
No vocal response to pain	0
Eye movement	
Watches or follows	1
Fails to watch or follow	0
Best total score	5

as an outcome. Within 1 hour of admission, all children had their ears examined through otoscopy and underwent tympanometry with the use of a handheld Kamplex tympanometer (Interacoustics A/S, Assens, Denmark). We classified tympanometry measurements as either normal (type A) or abnormal (types B or C) by using the Liden and Jerger criteria.[10] During care, we assessed for clinical features of increased ICP, defined as at least 2 of the following features: dysconjugate eye gaze, dilated unreactive pupils, decerebrate or opisthotonic posturing, papilledema as confirmed by 2 clinicians, irregular and shallow respiration, and evident Cushing's reflex (bradycardia associated with hypertension).[13] Cerebrospinal fluid (CSF) pressure was measured during routine lumbar puncture (LP), which was performed if children were clinically stable enough to tolerate the procedure. All children were recruited by the study clinicians (S.G. and E.C.) who conducted the study-related procedures, including otoscopy and tympanometry, and assessed the children for neurologic deficit at discharge from hospital. Clinical management was conducted uniformly for all children according to standard guidelines by duty clinicians who were not investigators in the study.[14–16]

We analyzed the data by using Stata software, version 11.0 (StataCorp LP, College Station, TX). We applied Kruskal-

Wallis equality of populations test for nonnormal continuous data and presented the results as medians and interquartile ranges (IQRs). We examined for associations between categorical data by using χ^2 and Fisher's exact tests as appropriate. From initial analysis of the primary TMD study data, we identified candidate risk factors univariably associated with death. We included these variables in a multivariable logistic regression model to examine for the independent association between tympanometry and mortality. We assessed for statistical significance at the conventional 5% level and reported results as odds ratio (ORs) and 95% confidence intervals (CIs).

RESULTS

Of 107 eligible children (Fig 1), we recruited 72 with a median age of 3.2 years (IQR: 2.0–4.3 years); 31 (43%) were female.[9] Thirty-eight (53%) had cerebral malaria (CM), 8 (11%) acute bacterial meningitis (ABM), 4 (6%) sepsis, and 22 (30%) encephalopathy of unknown etiology. Twenty (28%) children died during hospital stay, at a median time of 33 hours (IQR: 13–51 hours) from the time of admission. Children with ABM and sepsis were more likely to die compared with those with CM (OR: 7.4; 95% CI: 1.2–44.8 [P = .01] and OR: 13.3; 95% CI: 0.9–187.3 [P = .01], respectively) (Table 2). Twenty-nine children had clinical features of increased ICP. Children with clinical features of increased ICP had greater risk of death compared with those without increased ICP (OR: 12.0; 95% CI: 2.8–52.2; P < .01). No abnormalities were noted on otoscopy.

Tympanometry was normal in 25 (35%) children. Children with ABM and sepsis had lower tympanic membrane compliance compared with those with unknown encephalopathy or CM (P = .01) (Table 3). Overall, a greater proportion of children with ABM, sepsis, and unknown encephalopathy had ab-
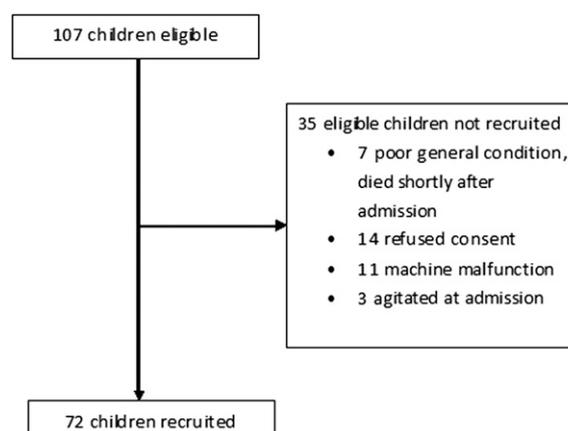
normal tympanometry compared with those with CM, although this finding was not significant. Children who died had lower tympanic membrane compliance compared with those who survived (Table 2). Adjusting for diagnosis and features of increased ICP, children with abnormal tympanometry had greater odds of death compared with those with normal tympanometry (adjusted OR: 17.0; 95% CI: 1.9–152.4; P < .01).

There was no difference in clinical features of increased ICP between those who had abnormal (n = 7; 28%) and those who had normal (n = 22; 47%; P = .12) tympanometry. Seven children with abnormal tympanometry had a median opening LP pressure of 12.5 cm (IQR: 9.0–17.5 cm) of water compared with 11.8 cm (IQR: 10.5–18 cm) in 3 who had normal tympanometry (P = .91).

FIGURE 1
Study flowchart.

TABLE 2 Summary Clinical Characteristics by Outcome

Parameter	Died (n = 20)	Survived (n = 52)	Odds Ratio (95% CI)	P
Age, median (IQR), y	2.3 (1.3–3.9)	3.6 (2.2–4.3)	—	.10
Gender				
Male	12	29	—	—
Female	8	23	—	.75
Duration of coma at presentation, median (IQR), h	2 (1–4)	4 (1–8)	—	.07
BCS				
2	10	36	—	—
1	7	14	1.8 (0.6–5.8)	.32
0	3	2	5.4 (0.7–40.3)	.06
Clinical features of increased ICP, n (%)	16 (80)	13 (52)	12.0 (2.8–52.2)	<.01
Diagnosis				
Cerebral malaria	7	31	—	—
Acute bacterial meningitis	5	3	7.4 (1.2–44.8)	.01
Sepsis	3	1	13.3 (0.9–187.3)	.01
Unknown encephalopathy	5	17	1.3 (0.4–4.8)	.69
Abnormal tympanometry, n (%)	19 (95)	28 (54)	—	<.01
Type A tympanogram (normal)	1	24	—	—
Type B tympanogram	14	22	15.3 (1.51–55.3)	<.01
Type C tympanogram	5	6	20 (1.33–11.9)	<.01
Tympanometry compliance, median (IQR), mL	0.29 (0.1–0.3)	0.48 (0.3–0.7)	—	<.01
Middle ear pressure, median (IQR), daPa	−120.5 (−218 to −14)	−47 (−144.5 to 3.0)	—	.22

Clinical features of increased ICP and abnormal tympanometry, sepsis, and ABM when compared with CM were univariably associated with death. daPa, deca Pascals.

TABLE 3 Tympanometry Parameters by Diagnosis

	Cerebral Malaria (n = 38)	Unknown Encephalopathy (n = 22)	Acute Bacterial Meningitis (n = 8)	Sepsis (n = 4)	P
Compliance, median (IQR), cm3	0.48 (0.31–0.73)	0.31 (0.15–0.57)	0.18 (0.03–0.41)	0.13 (0.06–0.28)	<.01
Middle ear pressure, median (IQR), daPa	−63 (−134 to −8)	−129 (−195 to −4)	42.5 (−123.5 to 138)	−80.5 (−123.5 to −45.5)	.24
Abnormal tympanometry, n (%)	20 (53)	16 (73)	7 (88)	4 (100)	.07

Children with ABM and sepsis had lower tympanic membrane compliance compared with those with unknown encephalopathy or CM. daPa, deca Pascals.

DISCUSSION

Our study reveals an unexpected finding of a significant association between abnormal tympanometry and death in children who had acute nontraumatic encephalopathy independent of etiology and clinical features of increased ICP. Specifically, children who died had significantly lower compliance than those who survived.

Low compliance is most commonly attributed to decreased mobility of the tympanic membrane due to middle ear effusion and increased stiffness of the eardrum due to scarring.[10] Abnormal compliance in children with nontraumatic encephalopathy in relation to mortality could be indicative of an intraaural origin of fatal intracranial pathology. Indeed, intracranial complications of otitis media have been well described and include meningitis, brain abscess and subdural empyema, meningocele, and pneumocephalus.[17–20] Conversely, it may also be a sign of pathology originating from the intracranial space extending to the inner and middle ear. Gross structural defects of the base of the skull may allow for this, predisposing individuals to a fatal outcome in the event of intracranial or upper airway diseases. Congenital bony defects in the inner and middle ear have been described in children in relation to recurrent occurrence of meningitis.[21] Less common is spontaneous leakage of the CSF into the middle ear, which has been described among adult patients.[22] This finding has been ascribed to nontraumatic defects on the tegmen of the temporal bone, thought to be either due to aberrant embryologic development of the tegmen or arachnoid granulations blind-ending into the temporal bone, which may erode due to CSF pressure and result in CSF leakage into the middle ear.[22] Such defects, perhaps more common in the general population than has been appreciated, may result in spread of intracranial pathology and transmission of ICP dynamics into the middle ear, or may allow for retrograde spread of infection from the middle ear.

Abnormal compliance may also indicate abnormal ICP dynamics transmitted to the middle ear. Indeed, some studies have demonstrated modification of middle ear acoustic impedance in response to increased ICP induced by jugular compression: the jugulotympanic reflex.[23,24] This reflex is absent in osteosclerotic patients in whom the cochlear aqueduct is not patent and transmission of ICP to the perilymphatic space is not possible.[23] Transmission of ICP through the cochlear aqueduct is the basis of function of the TMD analyzer technique whose utility we sought to establish as the main objective of our study.[9] However, we did not observe any significant relationship between tympanometry and TMD analyzer measurements or LP manometry readings and clinical features of raised ICP.[9] Only 10 children underwent LP manometry, and it is difficult to conclude on a lack of association between tympanometry and ICP measurements. It is also worth appreciating that LP manometry is most optimally measured over a period of at least 30 minutes, which was not sustainable in our severely ill, unventilated children.[8]

The plan to analyze admission tympanometry data was defined a priori to determine the baseline characteristics of the children recruited for the TMD analyzer study. Further reexamination of these tympanometry data was post hoc. However, the difference in admission tympanometry between those who died and those who survived is so compelling as to warrant reporting these findings, albeit in consideration of the limitations of such analysis. Our study highlights the need for prospective studies to investigate these significant findings, which have considerable potential for development of management strategies for coma. Such investigations should incorporate imaging studies of the cranium and the auricular system, provide repeat measurements beyond the time of admission alongside measurement of ICP, and take into account the different etiologies of nontraumatic coma. MRI, computerized tomography scans of the base of the skull and the brain, and radionucleotide tests may be useful in revealing structural defects and elucidating the relationship between middle ear function and ICP dynamics and outcome.[22,25] Potentially, because the tympanometer is relatively inexpensive and simple to use, it may greatly aid in monitoring and providing additional information on prognosis in children with acute coma, allowing for greater insights into the pathophysiology of childhood acute encephalopathies.

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