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Brain MRI Findings: In Neonates at Risk of Acute Bilirubin Encephalopathy in Relation to Gestational age, Weight and Bilirubin Level And Neurodevelopmental Outcome.

KEYWORDS: hyperbilirubinemia, BERA, MRI, acute bilirubin encephalopathy

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ABSTRACT *AIMS: To describe brain MRI findings in neonates at risk of acute bilirubin encephalopathy in relation to gestational age, weight and bilirubin levels, age at imaging and neurodevelopmental outcome.*
MATERIAL AND METHODS: Neonates with TSB >18 mg/dl. Review of neonatal data, at birth and later, MRI scans and BERA and neurodevelopmental outcome.
RESULTS: 22 neonates were studied, 2 < 31, 7 b/w 34–36 and 13 b/w 37–40 weeks GA. MRI showed abnormal SI in the BG in 14/22 at birth and 13/22 in later scans. Abnormal WM SI occurred in 12/22 at birth & 7/22 later scans. 13 infants developed motor/auditory sequelae. Adverse outcome was associated with high SI in BG (7/13) on late T2-weighted MRI (all GA) and abnormal BERA on follow up. WM and STN abnormalities, did not correlate with outcome.
CONCLUSIONS: Severe sequelae occurred with relatively low TSB levels in preterm but at high levels in terms. In asymptomatic patients at presentation, follow up MRI and BERA can reliably predict abnormal neurodevelopment outcome.

Introduction
The serum unconjugated bilirubin levels of most newborn infants rises to >2mg/dl in first week life. This level usually rises in full term infants to a peak of 6-8 mg/dl by 3-5 days of age then falls. A rise to 12mg/dl is in the physiological range.In premature infants the peak may be 10 to 12 mg /dl on the 5th day of life, possibly rising >15 mg/dl without any specific abnormality of bilirubin metabolism[1]. Extreme hyperbilirubinemia causes bilirubin encephalopathy and toxicity to basal ganglia and brainstem nuclei, rare but preventable cause of severe, morbidity in otherwise normal infants.

Acute bilirubin encephalopathy is the clinical manifestation of bilirubin toxicity seen in the neonatal period[1,2]. Kernicterus is a pathologic diagnosis and refers to yellow staining of the brain by bilirubin together with evidence of neuronal injury[2,3,4].

The classic signs of acute bilirubin encephalopathy in the severely hyperbilirubinemic term infants include increasing hypertonia, especially of extensor muscles,with retrocolis, opisthotonus, in association with varying degrees of drowsiness, poor feeding, hypotonia, and alternating tone.

Aims
To describe magnetic resonance imaging (MRI) findings in neonates at risk of acute bilirubin encephalopathy, in relation to Gestational age, Total serum bilirubin and Age at imaging.

To assess the clinical neurological outcome.

METHOD
A prospective hospital based study was carried out at a tertiary care centre in north India from October 2011 to September 2013.

Study group 40 cases in G.S.V.M. Medical College, who were either extremely preterm, preterm or term, with neonatal hyperbilirubinaemia selected for study out of these 30 neonates with neonatal hyperbilirubinaemia fulfilled the inclusion criteria, however 3 neonates died shortly after birth, hence study group comprised of 27 neonates. 5 infants defaulted on follow up, henceforth 22 neonates comprised the final study group.

INCLUSION CRITERIA
Neonates with hyperbilirubinemia.

Extremely preterm <32 wks of GA (serum bilirubin >18 mg/dl).

Preterm 32 1/7 to 36 6/7 wks of GA (serum bilirubin >18 mg/dl).

Term 37 to 41 6/7 wks of GA (serum bilirubin >20 mg/dl).

Neonates with acute bilirubin encephalopathy.

EXCLUSION CRITERIA
1. Neonates with any congenital malformations.

2. Neonates with apgar scores <6 at 1 and 5 minutes of life.

3. Neonates with delayed cry with or without cyanosis.

4. Neonates requiring endotracheal intubation and manual IPPV for at least 1 to 5 minutes after birth.

5. Neonates with any systemic diseases and hypoxic ischemic encephalopathy with potential negative influences on neurological development.

STUDY METHOD
Informed consent was taken from attendants of all patients and permission was taken from ethical committee of institution.

Neonates with were divided into 3 categories based on GA

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1. Extremely preterm <32 wks of GA.

2. Preterm 32 1/7 to 36 6/7 wks of GA.

3. Term 37 to 41 6/7 wks of GA.

In preterm neonates cases with total serum bilirubin levels>18 mg/dl and in term neonates cases with total serum bilirubin levels>20 mg/dl with or without signs and symptoms of acute bilirubin encephalopathy were incorporated in the study.

All neonates were reviewed for

Apgar scores.

Age at admission.

Level and age of maximum TSB.

Evidence of acidosis sepsis and other pathologies.

Neonatal clinical signs /symptoms.

Neurological examination at presentation and up to 1 year

Results of brain imaging MRI at presentation and at follow up (6 MONTHS).

Results of BERA (auditory assessment) at presentation and at follow up (6 MONTHS).

RESULTS

From the above study conducted at a tertiary care centre from October 2011 to September 2013, analyzing a population of 22 neonatal hyperbilirubinaemia cases using serial MRI and BERA and on follow up assessing their neurodevelopmental outcome, following results were obtained.

MRI findings in relation to gestational age; both in term and preterm neonates there is approximately equal distribution of abnormalities in GP (globus pallidus), STN (sub thalamic nuclei) and WM (white matter), whereas in extremely preterm neonates abnormalities in STN were found to a lesser degree as compared to preterm and term neonates.(table 1,2,3)

MRI findings in relation to maximum serum bilirubin levels; we found that TSB levels did not correlate with MRI findings neither in extremely preterm, preterm or term neonates.

MRI findings in relation to age at scan; we found a consistent scan evolution of MRI irrespective of gestational age with earlier T1 abnormalities being replaced by T2 abnormalities in follow up scans.

MRI findings in relation to neurodevelopmental outcome; in our study we did not find a significant correlation between MRI findings and abnormal neurodevelopmental outcome.

MRI findings do reverse to normal in few neonates on therapy on follow up and that most neonates who had persistent signal intensity (SI) on follow up at 6 months usually had it in T2 weighted images.(table 6)

Normal BERA at presentation does not herald a normal hearing on follow up at 1 year and that abnormalities in BERA can occur later on by 6 months of age predicting an abnormal auditory outcome in infancy as determined by BERA at 1 year.(table 4,5)

In our study we found that initial abnormalities in BERA can revert back to normal on treatment and that an initial normal BERA does not predict a normal hearing at infancy.

In our study we also found that performing BERA on 6 months follow up showed more significant correlation to hearing loss at 1 year than doing it at presentation.

In our study we found that occurrence of sequelae on follow up was inversely proportional to gestational age and birth weight and occured at lower serum bilirubin levels.

Presence or absence of features of acute bilirubin encephalopathy at presentation was independent of neurodevelepmental outcome. On the contrary cases with signs and symptoms of bilirubin encephalopathy at presentation could have a normal neurodevelopmental outcome on follow up.(table 7)

DISCUSSION

Despite various advances in management and diagnosis of acute bilirubin encephalopathy, it is the subtle nature of Bilirubin Induced Neurological Dysfunction (BIND) and an early hospital discharge, that is causing re-emergence of chronic bilirubin encephalopathy and is having an implication on long term neurodevelopmental status of a neonate.

Above concerns lead to the pressing needs of newer diagnostic evaluation that allow diagnosis of BIND at an age where interventions can improve the outcome. This study was conducted for a complete evaluation of acute bilirubin encephalopathy and assessing the usefulness of MRI and ABER in early prediction of an abnormal outcome.

In term and preterm neonates there is approximately equal distribution of abnormalities in BG, STN and WM whereas in extremely preterm neonates abnormalities in STN were found to a lesser degree as compared to preterm and term neonates unlike other study as conducted by **Meropi T et al, (2008)[5]**.

In our study we found that brain MRI follows a chronological sequence. In the ***first phase (acute phase)***, we detect a signal increase in T1-weighted sequences in globus pallidus and not in the subthalamic nuclei as suggested by **Yokochi K et al, (1995)[6], Steinborn M et al, (1999)[7]**. We believe that these findings reflect the immediate astroglial reaction to insult, oedema or the presence of bilirubin as also suggested by **Govaert P et al, (2003)[8] , Yilmaz Y et al, (2002)[9]** and **Yilmaz Y et al, (2001)[10]**. During a ***second (transitional) phase***, the hyperintensity in the T1-weighted images decreases throughout the second and third weeks of life before becoming normal. Increase in signal intensity in T2-weighted images have been described at 6 to 8 days after birth by **Govaert P et al, (2003)[8]** and **Penn AA et al, (1994)[11]**. Neuroimaging findings evolved similarly in all cases observed. The hyperintensities in T1 weighted images practically disappeared, and then appeared in T2 weighted images in the globi pallidi, and not in the subthalamic nuclei as suggested by **Meropi T et al, (2008)[5]**. **Yokochi Y et al, (1995)[6]** showed that in ***third stage (the chronic phase)***, a hyperintense signal is identified in T2 which remains for the rest of the patient's life, and has been found in children as old as 12 years of age. This signal is indicative of the dense fibrillar gliosis with a low

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cellular content appearing in the final phase. Similarly our study showed persistence of abnormal T2 signal intensities however our follow up lasted only for one year.

Hansen TW et al,[12] suggested that not all neonates with hyperbilirubinaemia and abnormal neurological signs and symptoms in the neonatal period will develop the disease in future. However in our study we found that a patient would have a very high probability of developing BIND, if the neonate has clinical symptoms and signs suggestive of bilirubin encephalopathy together with abnormal biochemical parameters, neuroimaging and BERA findings. For this reason, we consider brain MRI and BERA to be a useful tool for determining bilirubin toxicity during the neonatal period and infancy.

The presence of hyperbilirubinaemia associated with suggestive clinical symptoms and abnormal MRI findings (initially, hyperintensity in the globi pallidi in T1 images, with subsequent hyperintensity in T2), together with abnormal BERA activity, allows us to establish an early diagnosis and an early initiation of treatment.

In our study it was found that MRI findings of GP do reverse to normal in 36% of neonates on follow up and all of the remaining neonates showed persistent signal intensity (SI) in T2 weighted images on follow up.

We were not able to show a consistent relationship between early imaging abnormality and motor outcome but on later scans 76% of neonates with abnormal motor outcome had classic changes in the globus pallidus (GP) on T2-weighted images, although the p value for the above correlation was not significant as also suggested by **Mustafa MT et al, (2010)[13].**

We also observe that at peak of TSB, the term neonates presented with typical signs of acute bilirubin encephalopathy as also mentioned in **Volpe JJ Neurology of the newborn, 4th edition, (2001)[14].** Whereas the preterm neonates in our study had apnoeic episodes and desaturations, supporting a distinctive picture of hyperbilirubinaemia in the preterm population as also suggested by **Govaert P et al, (2003)[8]**. Apnoeas have been attributed to brainstem dysfunction caused by bilirubin.

The most frequent underlying diagnosis in present study was ABO/Rhesus incompatibility (36%). However in one third of neonates obvious aetiology could not be established as suggested by **Shapiro SM et al, (2003)[15]**.

In our study, there was a consistency of scan evolution, confirming the usefulness of SI abnormality in the GP on T1-weighted early MR scans and of the early combination of abnormal SI on T1W and on T2W images (at least as subtle changes) in preterm and term infants as described previously. However, abnormal late scans were preceded by normal scans in four preterm neonates. In term or near term infants, possibly because of increased brain metabolic rate, changes were seen within 2 days to 4 weeks after peak TSB.

On the other hand we also saw that few neonates with abnormal initial scans became normal on follow up. This could reflect a contribution from oedema to imaging changes in the acute stage which resolved later.

In our study in term neonates only 61% of early and 37% of follow up scans had an abnormal appearance to the STN. The STN is not always easy to identify as it depends on plane and level of imaging and thin slices are required not to miss the nuclei on coronal T2 images used for follow-up. Abnormality in the STN may help confirm the diagnosis of bilirubin encephalopathy as suggested by **Govaert P et al, (2003)[8], Penn AA et al, (1994)[11]**, **Steinborn M et al, (1999)[7]**. STN abnormality occurence in term neonates with severe hearing loss was described by above authors in their studies. No similar correlation has been seen in our study.

We also observed that though the term neonates had an abnormally high peak TSB levels, it did not correlate with either MRI or BERA findings at presentation, on follow up and with hearing loss, hitherto reported **Newman TB et al, (1992)[16]**. As with term neonates and also suggested by previous studies **Govaert P et al, (2003)[8], Harris MC et al, (2001)[17], Okumura A et al, (2001)[18], Steenweg ME et al, (2010)[19], Sugama S et al, (2001)[20], Yilmaz Y et al, (2001)[10]**, similarly in preterm neonates TSB levels did not correlate with MRI/BERA findings at presentation, on follow up and with hearing loss.

In conclusion we found a wider spectrum of MRI findings both in preterm and term infants with ABE (acute bilirubin encephalopathy) kernicterus than previously reported. The occurrence of neurological damage at relatively low TSB levels in preterm infants highlights the need for further study on the effects of GA, the rate of rise and duration of hyperbilirubinaemia, and other neonatal risk factors to identify infants at risk for neurotoxicity. The reasons for the late appearance of classic changes in the GP and the aetiology and significance of the changes we found in the WM are unclear. Our data, though limited by its small patient number, shows that MRI scans at presentation were not reliable in excluding significant damage to the GP and we suggest that an MRI scan at least at 6 months post term age is needed when kernicterus is suspected. More detailed imaging in a larger group of infants using sequential diffusion weighted imaging from the time of TSB and MRI at an older age might elucidate further a structural and functional relationship and help in understanding the pathological processes and developmental difficulties experienced by these neonates.

Hyperbilirubinaemia is a significant risk factor for auditory neuropathy/dysynchrony diagnosed as hearing loss of variable severity and configuration with recordable OAE or cochlear microphonic (CM) responses but absent or atypical BERA as suggested by **Agarwal VK et al, (1998)[21]**. In our study hearing loss and TSB levels did not correlate and neonatal BERAs were not predictive of future HL (p value >.05) on follow up, as previously documented **Yilmaz Y et al, (2001)[9]**. We also found that normal BERA at presentation does not herald a normal hearing on follow up at 1 year, and that abnormalities in BERA can occur later on by 6 months of age predicting an abnormal auditory outcome in infancy as determined by BERA at 1 year (p value < .05).

We would also like to suggest that initial abnormalities in BERA can revert back to normal on treatment and that an initial normal BERA does not predict a normal hearing at infancy. 2 out of the 22 cases with normal BERA on 6 months follow up went on to develop hearing loss as determined by BERA at 1 year. These findings could not be explained and require detailed evaluation for other causes of hearing loss. This may be due either to normalization of ABER after exchange transfusion or phototherapy, misin-

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terpretation of "Giant" CM responses as normal ABR responses or to preservation of some of the inner hair cells allowing persistence of an BERA response as suggested by **Shapiro SM et al, (2003)[22]**.

To conclude, BERA detects subclinical bilirubin encephalopathy even before appearance of any sign or symptoms of kernicterus as observed in the present study. Thus serial BERA may be a useful, non invasive, cost effective and radiation free tool to detect neurodevelopment delay secondary to hyperbilirubinemia.

CONCLUSION

From our study we concluded that in cases of neonatal hyperbilirubinemia MRI findings showed a consistent scan evolution from T1 to T2 weighted images and that there was not much of a difference in MRI finding in preterm and term neonates, however extremely preterm cases conspicuously showed absence of STN changes, a finding which needs further studies with a large sample size for confirmation of the finding and evaluation of the reason.

Severe neuromotor sequelae occurred with relatively low TSB levels in preterms but only at high levels in full terms and in neonates with more birth weight, the causes of increased susceptibility of preterm neonates to a lower serum bilirubin level need to be defined and included in the management protocols of neonatal hyperbilirubinemia.

BERA detects subclinical bilirubin encephalopathy even before appearance of any sign or symptoms of kernicterus as observed in the present study. Thus serial BERA may be a useful, non invasive, cost effective and radiation free tool to detect neurodevelopment delay secondary to hyperbilirubinemia.

We also found that if at presentation signs and symptoms of bilirubin encephalopathy are not present, it is prudent to perform MRI and BERA on follow up to predict an abnormal neurodevelopmental outcome, since absence of clinical features does not predict a normal neurodevelopmental outcome.

TABLE: 1
MRI FINDINGS IN EXTREMELY PRETERM NEONATES AT PRESENTATION AND ON FOLLOW UP AT 6 MONTHS
n =2

S NO.	GLOBUS PALLIDUS		STN		WHITE MATTER	
	T1	T2	T1	T2	T1	T2
ON PRESENTATION						
Normal	2	2	2	2	1	0
Abnormal	0	0	0	0	1	0
ON 6 MONTHS FOLLOW UP						
Normal	1	0	2	2	2	0
Abnormal	1	2	0	0	0	2

TABLE: 2
MRI FINDINGS IN PRETERM NEONATES AT PRESENTATION AND ON FOLLOW UP AT 6 MONTHS
PRETERM n=7

SERIAL NO	GLOBUS PALLIDUS		STN		WHITE MATTER	
	T1	T2	T1	T2	T1	T2
ON PRESENTATION						
Normal	3	5	3	5	4	3
Abnormal	4	2	4	2	3	4
ON 6 MONTHS FOLLOW UP						
Normal	5	3	7	4	7	4
Abnormal	2	4	0	3	0	3

TABLE: 3
MRI FINDINGS IN TERM NEONATES AT PRESENTATION AND ON FOLLOW UP AT 6 MONTHS
TERM n=13

SERIAL NO.	GLOBUS PALLIDUS		STN		WHITE MATTER	
	T1	T2	T1	T2	T1	T2
ON PRESENTATION						
Normal	4	7	5	8	7	5
Abnormal	9	6	8	5	6	8
ON 6 MONTHS FOLLOW UP						
Normal	11	6	12	9	13	4
Abnormal	2	7	1	4	0	9

TABLE: 4
RELATIONSHIP OF BERA WITH HEARING LOSS

S.NO.	AT PRESENTATION	AT 6 MONTHS	OUTCOME BERA AT 1 YEAR
EXTREMELY PRETERM n=2			
1	N	A	HL
2	A	N	No HL
PRETERM n=7			
1	N	A	HL
2	N	A	HL
3	N	N	No HL
4	N	N	No HL
5	A	A	No HL
6	A	A	HL
7	A	A	No HL
ASSOCIATION OF BERA WITH HEARING LOSS n=13 TERM			
1	N	A	HL
2	N	N	HL
3	N	N	No HL
4	A	A	HL
5	N	N	No HL
6	A	N	No HL
7	A	N	No HL
8	A	N	No HL
9	A	N	HL
10	A	A	HL
11	A	N	No HL
12	A	A	No HL
13	A	A	No HL

A= Abnormal, N= Normal, HL= Hearing loss

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TABLE: 5
ASSOCIATION OF BERA AT PRESENTATION AND AT AT 6 MONTHS WITH OUTCOME
n=22

	NUMBER OF CASES			
BERA	At presentation		At 6 month	
	OUTCOME		OUTCOME	
	GOOD	POOR	GOOD	POOR
NORMAL	4	5	9	2
ABNORMAL	9	4	3	8

Significant association of BERA at 6 months with outcome (p value <.05).

TABLE: 6
ASSOCIATION OF MRI AT PRESENTATION AND AT AT 6 MONTHS WITH OUTCOME n=22

	NUMBER OF CASES			
MRI	At presentation		At 6 month	
	OUTCOME		OUTCOME	
	GOOD	POOR	GOOD	POOR
NORMAL	5	3	6	3
ABNORMAL	6	8	3	10

Above table shows that there is no significant association of MRI at presentation and at at 6 months with outcome (p value >.05). CHI SQUARE TEST

TABLE: 7
ASSOCIATION OF NORMAL CLINICAL PROFILE AT PRESENTATION WITH OUTCOME n=22

NUMBER OF CASES		
ACUTE BILIRUBIN ENCEPHALOPATHY	OUTCOME	
	NORMAL	ABNORMAL
ABSENT	5	7
PRESENT	4	6

References

1. Cloherty JP, Eichenwald EC, Hansen AR, Stark AR, manual of neonatal care, 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2012.
2. Bhutani VK, Johnson L. Kernicterus: A preventable neonatal brain injury. J. Arab Neonatal Forum 2005; 2: 12-24.
3. Jones MH, Sands R, Hyman CB, Sturgeon P, Koch FP. Longitudinal study of the incidence of central nervous system damage following erythroblastosis fetalis. Pediatrics 1954;14:346.
4. Van Pragh R. Diagnosis of kernicterus in the neonatal period. Pediatrics 1961;28: 870-874.
5. Meropi T, Gkoltsiou K, Counsell S, Rutherford M, Cowan F. Serial brain MRI and ultrasound findings: relation to gestational age, bilirubin level, neonatal neurologic status and neurodevelopmental outcome in infants at risk of kernicterus. Early human development. 2008 Dec;84(12):829-38.
6. Yokocki K. Magnetic resonance imaging in children with kernicterus. Acta Paediatr 1995;84:937–9.
7. Steinborn M, Seelos KC, Heuck A, von Voss H, Reiser M. MR findings in a patient with kernicterus. Eur Radiol 1999;9:1913–5.
8. Govaert P, Lequin M, Swarte R, Robben S, De Coo R, Weisglas-Kuperus N, et al. Changes in globus pallidum with (pre) term kernicterus. J Pediatrics 2003;112:1256–63.
9. Yilmaz Y, Ekinci G. Thalamic involvement in a patient with kernicterus. Eur Radiol 2002;12:1837–9.
10. Yilmaz y, Alper G, Kiliçoglu G, Celik L, Karadeniz L, Yilmaz-Değirmenci S Magnetic resonance imaging findings in patients with severe neonatal indirect hyperbilirubinemia. Journal of Child Neurology (impact factor: 1.75). 07/2001; 16(6):452-5.
11. Penn AA, Enzmann DR, Hahn JS, Stevenson DK. Kernicterus in a full term infant. Pediatrics 1994;93:1003–6.
12. Hansen TW. Mechanisms of bilirubin toxicity: clinical implications. Clin Perinatol 2002;29(4): 765-778.
13. Mustafa MT, Ahmet karadağ, Ender ödemiş, Sumeyye sarraoğlu, Mehmet yörübulut. The role of magnetic resonance imaging in the prediction of the neurodevelopmental outcome of acute bilirubin encephalopathy in newborns. Turk J Med Sci. 2009; 39(4): 507-511.
14. Volpe JJ. Bilirubin and brain injury. In: Neurology of the Newborn. 4th Edition, 2001.
15. Shapiro SM. Bilirubin toxicity in the developing nervous system. Pediatr Neurol 2003;29(5):410-421.
16. Newman TB, Maisels MJ. Evaluation and treatment of jaundice in the term newborn: a kinder, gentler approach. Pediatrics 1992;89:809-18.
17. Harris MC, Bernbaum JC, Polin JR, Zimmerman R, Polin RA. Developmental follow up of breastfed term and near term infants with marked hyperbilirubinemia. Pediatrics 2001;107:1075–80.
18. Okumura A, Hayakawa F, Kato T, Itomi K, Mimura S,Watanabe K. Preterm infants with athetoid cerebral palsy: kernicterus? Arch Dis Child Fetal Neonatal Ed. 2001 March; 84(2): F136–F137.
19. Steenweg ME, Vandrver A, Blaser S, Bizzi A, de Koning TJ, Mancini GM, Van Wieringen WN, Barkhof F, Wolf NI, Van der Knaap MS. Magnetic resonance imaging (MRI) of kernicterus and bilirubin-induced neurological dysfunction (BIND). Brain. 2010 Oct;133(10):2971-2982.
20. Sugama S, Soeda A, Eto Y. Magnetic resonance imaging in three children with kernicterus. Pediatr Neurol 2001;25:328–31.
21. Agrawal VK, Shukla R, Misra PK, Kapoor RK, Malik GK. Brainstem auditory evoked response in newborns with hyperbilirubinemia. Indian pediatrics. 1998 Jun;35(6):513-8.
22. Shapiro SM. Bilirubin toxicity in the developing nervous system. Pediatr Neurol 2003;29(5):410-421.