Original Articles

Aetiology of global developmental delay in young children: Experience from a tertiary care centre in India

ANURAG TIKARIA, MADHULIKA KABRA, NEERJA GUPTA, SAVITA SAPRA, PRAHLAD BALAKRISHNAN, SHEFFALI GULATI, R. M. PANDEY, A. K. GUPTA

ABSTRACT

Background. Global developmental delay is a common reason for referral to a paediatrician. We examined the aetiological yield of an extensive diagnostic work-up in young children with developmental delay in a tertiary referral centre.

Methods. To assess the diagnostic possibilities, we systematically examined 100 consecutive children with global developmental delay (< 5 years of age) who visited the paediatric outpatient department over a period of 18 months. An association between the presence of features at initial contact and aetiology was analysed by the 2-tailed Fisher exact test and chi-square test.

Results. Of the 100 children, 65 were < 2 years of age (mean age 23.6 months) at presentation. The presence of birth asphyxia, sepsis, seizures, abnormal neurological findings, and dysmorphism were significant predictors of aetiology. Four diagnostic categories—chromosomal disorders including Down syndrome, hypoxic–ischaemic encephalopathy, multiple malformation syndromes and cerebral dysgenesis—were the most common causes of global development delay in 20%, 15%, 14% and 11%, respectively. Moderate delay was seen in 42%, severe in 33% and mild in 25% of the patients. The aetiological yield did not differ with the severity of global developmental delay. Additional investigations such as neuroimaging, cytogenetic analysis, metabolic tests and specific molecular tests contributed to a diagnosis in 73% of the children, while in 23% these were the sole means of arriving at a diagnosis. Neuroimaging for a specific indication was almost twice more likely to yield an aetiology when compared with neuroimaging performed as a screening tool (65% *v.* 35%; p = 0.003).

Conclusion. The aetiological yield in this selected cohort with global developmental delay was 73%. A step-wise investigational approach is justified in all children with developmental delay, regardless of the severity of delay or the absence of findings on history and physical examination. This study is an attempt to formulate an investigative approach in a child with global developmental delay, especially in developing countries where advanced molecular and cytogenetic studies are not routinely available.

Natl Med J India 2010;23:324–9

All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110029, India

ANURAG TIKARIA, MADHULIKA KABRA, NEERJA GUPTA, SAVITA SAPRA, PRAHLAD BALAKRISHNAN, SHEFFALI GULATI Department of Paediatrics

R. M. PANDEY Department of Biostatistics

A. K. GUPTA Department of Radiodiagnosis

Correspondence to MADHULIKA KABRA; *madhulikakabra@hotmail.com*

INTRODUCTION

Developmental delay is one of the most common conditions encountered by paediatricians in clinical practice. Early identification and diagnosis have implications for treatment (as in congenital hypothyroidism), genetic counselling and estimation of the risk of recurrence, management of possible associated conditions, prognostication and prevention, both at the individual and community level.[1]

Despite its frequency and huge impact on society, controversy still exists regarding the appropriate clinical and laboratory investigations needed to understand the causes of developmental delay.[2] However, there is a consensus that a blanket, unfocused approach is not warranted though the choice of investigations remains unclear and there is a need for better standardization.[3]

To determine the aetiology of mental retardation, large diagnostic studies have been undertaken. These have shown that mental retardation is heterogeneous and the aetiology is still unknown in 20%–50% of the severe forms and 5%–10% of the mild forms.[4] The aetiological frequencies are quite varied and have been explained by differences in setting, degree of mental retardation, patient selection criteria, study protocols, technological advances over time, and definitions of diagnoses.[5,6]

We studied the aetiological profile of young children with developmental delay in India, and the yield of diagnostic evaluation in these children.

METHODS

Global developmental delay (GDD) was defined as a significant delay in 2 or more developmental domains (gross/fine motor, cognition, speech/language, personal/social, or activities of daily living). Significant delay was defined as performance that was 2

or more standard deviations (SD) below the mean on norm-referenced developmental screening or assessment tests.[1] GDD was classified as mild if the development quotient (DQ) was 55–69, moderate if the DQ was 40–54 and severe if it was <40.[1]

Over a period of 18 months, we enrolled 100 consecutive children with GDD, 6 months to 5 years old, who visited our paediatric outpatient department and specialty clinics (Genetics, Neurology and Developmental clinics). Children with suspected developmental delay not confirmed on formal developmental assessment, those with delay in only one developmental domain, acute postnatal event with initial normal development and regression of milestones were excluded from the study. Children with suspected autism without associated dysmorphism were also excluded. Informed consent was obtained for participation in the study. At initial assessment, a pre-designed proforma that included demography, history and physical examination was completed for each subject. A detailed history, including prenatal risk factors, perinatal complications and postnatal events, along with family and social history, was taken. A thorough general physical examination with anthropometry, detailed evaluation for congenital anomalies, and systemic examination including a complete neurological and ophthalmic examination was done (Table I). A child psychologist performed developmental assessment including calculation of developmental age and quotient using the Bayley development schedule for those 0–3 years of age, Stanford–Binet test for those >3 years of age, and Vineland social maturity scale for all ages.

TABLE I. Characteristics of the study population (*n*=100)

Characteristic	*n*
Mean (SD) age at evaluation (months)	23.6 (15)
Gender (M:F)	2:1
Severity of mental retardation	
Mild	25
Moderate	42
Severe	33
Positive historical features	67
Maternal age at conception >35 years	7
Preterm delivery	13
Caesarean section	20
Antenatal drug exposure	2
Antenatal exposure to infection	8
Bad obstetric history	10
Hospital delivery	38
Birth asphyxia (delayed cry >5 minutes and/or APGAR score at 1 minute <7)	20
Low birth weight	26/56 (46%)
Jaundice	12
Sepsis	5
Seizures	14
Stay in nursery	13
Positive family history	19
Consanguinity	3
Autistic features	6
Positive examination findings	78
Microcephaly	34
Macrocephaly	2
Failure to thrive	21
Short stature	12
Tall stature	1
Dysmorphism	70
Specific dysmorphism	44
Neurological abnormality	49
Increased tone	29
Decreased tone	20

Neuroimaging (computed tomography/magnetic resonance imaging [CT/MRI]) was done for all children with suspected hypoxic–ischaemic encephalopathy (HIE), suspected intrauterine infections, seizures, micro- or macrocephaly or abnormal head shape, focal neurological abnormality, and syndromes known to be associated with central nervous system (CNS) anomalies. Karyotyping was done for all the children with a family history of mental retardation, dysmorphism and/or multiple malformations. Molecular studies for fragile X syndrome were done on clinical suspicion. A search for recognizable congenital malformation syndromes was done in all children with unexplained dysmorphic features using the London dysmorphology database (LDDB).

Metabolic work-up (estimation of arterial blood gas, arterial lactate, urine and plasma amino acids, plasma ammonia and urine organic acids) was done in children with unusual hair, skin colour or odour, sepsis-like presentation with a negative septic screen, refractory vomiting, suggestive family history, unexplained seizures, cataract, hepatosplenomegaly and recurrent episodes of altered sensorium or acidosis.

An electroencephalogram (EEG) was done for all children with a history of seizures. Hearing evaluation including brainstem-evoked response audiometry (BERA), ophthalmic evaluation including fundus examination and thyroid function tests were done for all the children. Other investigations were done based on the clinical rationale.

Statistical analysis

The data were managed in Microsoft Excel and descriptive statistics on the population of interest were generated from the data obtained. An association between the presence of features at initial contact and aetiology was analysed by the 2-tailed Fisher exact test and chi-square test.

RESULTS

The mean (SD) age at presentation was 23.6 (15) months and the gender ratio was 2:1 (M:F). A positive history was present in 67 and examination was positive in 78 (Table I).

Investigations

Neuroimaging was done in 95 patients (CT scan in 88, MRI in 19, both in 12). Abnormalities were detected in 50 patients (53%); diffuse cerebral atrophy in 16 (35%), evidence of HIE in 12 (27%; multiple infarcts, periventricular leukomalacia, encephalomalacia, porencephalic cyst and gliotic focus), CNS malformations in 10 (22%) including corpus callosal agenesis in 3, cerebellar hypoplasia in 2, Dandy–Walker cyst in 2 and schizencephaly, semilobar holoprosencephaly and pachygyria in 1 each (Table II). Ventriculomegaly was seen in 6 (13%) and intracranial calcification in 5 (11%) patients. Both CT scan and MRI were done in 12 patients. Of these, 6 had abnormal and 4 had normal findings on both the tests. One patient had a normal MRI but intracranial calcification on CT and another had pachygyria on MRI but a normal CT scan. Thus, MRI was able to detect 1/12 (8.3%) additional anomalies not picked up by CT scan.

Karyotyping was done in 93 patients and was abnormal in 17. Thirteen (14%) had trisomy 21 and 4 had structural abnormalities (46,XY del 11p; 46,XX del 15q; 46,XY,t[2;5][q21;q11] and duplication 4q).

Aetiology

Based on the history, physical examination and selected laboratory investigations, an aetiological diagnosis was made in 73 of the

100 patients (Table III). Four diagnostic categories—chromosomal disorders including Down syndrome (20%), HIE sequelae (15%), multiple malformation syndromes (14%) and cerebral dysgenesis (11%)—accounted for 55 of the 73 diagnoses (75%) made.

Relationships

Evaluation of the relationship between features evident from the initial history and physical examination and the aetiological diagnosis showed that a history of birth asphyxia, sepsis or seizures increased the likelihood of ascertaining the aetiology from 1.4- to 2.4-fold, the maximum being with a history of birth asphyxia (Table IV). The presence of autistic features in the history was a negative predictor of aetiology (in only one-sixth could the aetiology be found compared with 72/94 with GDD without autism, p<0.005). Among 6 children with autistic features, a clinical diagnosis of Prader–Willi syndrome was made in 1 child, dysmorphism in 3 and basal ganglia calcification in 1. However, Prader–Willi syndrome could not be confirmed by molecular analysis. Abnormal examination findings such as microcephaly, specific features of dysmorphism and abnormal neurological examination increased the aetiological yield by 2.3-fold. Positive features on neurological examination were a strong and significant predictor of diagnostic yield (p<0.003). When stratified according to severity of delay, the aetiology could be determined in 18 of 25 (72%) with mild delay, in 29 of 42 (69%) with moderate delay, and 26 of 33 (78%) with severe delay. The yield across the three categories of delay was relatively constant (p=0.636).

TABLE II. Frequency of abnormalities in various investigations

Investigation	*n*	Abnormalities *n (%)*
Neuroimaging	95	50 (53)
MRI	19	12 (63)
CT scan	88	44 (50)
Both CT and MRI	12	6 (50)
Metabolic tests*	24	4 (17) (generalized aminoaciduria, Leigh disease, mucopolysaccharidosis and homocystinuria)
Karyotyping	93	17 (18.2)
Molecular studies for fragile X syndrome	1	1
Ophthalmic examination		
Abnormal fundus	100	19 (19) (optic atrophy, chorioretinitis)
Refractory errors		7
Cataract		4
Glaucoma		1
Others		
Brainstem-evoked auditory response	100	20 (20)
Thyroid profile (hypothyroidism)	100	3 (3)
EEG*	15	8 (50)

* for specific indications

TABLE III. Aetiology ascertained after investigations

Aetiology	*n*
No diagnosis made/idiopathic	27
Chromosomal	17
Sequelae of hypoxic–ischaemic encephalopathy	15
Syndromic	14
Central nervous system malformation	11
Monogenic (fragile X syndrome)	1
Metabolic disorder	4
Hypothyroidism	3
Down+hypothyroid	2
Environmental	
Intrauterine infection	4
Bilirubin encephalopathy sequelae	1
Toxin exposure (foetal valproate syndrome)	1
Total	100

Diagnostic yield

The diagnostic yield of neuroimaging for a specific indication was almost twice as likely to yield an aetiology when compared with neuroimaging performed as a screening tool (65% *v.* 35%; p=0.003). Karyotyping for a specific indication was 8 times more likely to yield a chromosomal abnormality as compared with karyotyping for screening (34% *v.* 4.4%; p=0.001). However, after exclusion of Down syndrome as a specific indication, the diagnostic yield was only twice as much (8.8% *v.* 4.3%).

History alone was insufficient in making a diagnosis in all the children. However, history and physical examination combined (which included an LDDB search) allowed a diagnosis to be made in 19 of 73 children (27%). In 54 of 73 (73%) cases in which an aetiology was determined, laboratory investigations contributed to the diagnosis and, in 17 of 73 (23%), laboratory investigations were the sole means of ascertaining the aetiology. All three—history, physical examination and laboratory investigations—were required for diagnosis in 37 of 73 children (50%).

The impact of determining the aetiology, beyond understanding the specific pathogenesis, was apparent in 31 of 73 children (42%). In 6 of 73 (8.2%), a specific medical or surgical management was possible, while in 25 of 73 (34%), a specific diagnosis helped in estimating the risk of recurrence in future pregnancies. Furthermore, 21 of 73 (28%) had a potentially preventable cause (HIE, toxins and infections). Among 20 children with a history of birth asphyxia, only 13 (65%) had neurological features and neuroimaging findings consistent with those of HIE sequelae. Thus, a history of birth asphyxia cannot be blindly taken as being responsible for developmental delay. One child had findings of cerebral dysgenesis on neuroimaging. Another child had primary microcephaly with possibly autosomal recessive inheritance. Two other children had other associated dysmorphisms fitting them into one of the recognized dysmorphology syndromes. No aetiology could be determined in 3 of 20 (15%) children with a history of birth asphyxia.

DISCUSSION

The importance of establishing a diagnosis in children with developmental delay has been highlighted earlier.[2,3] As is evident from the review of the literature, a consensus regarding the appropriate laboratory and clinical evaluation for this problem has been reached.[5,7] However, no Indian study on comprehensive evaluation of young children with GDD has been done in the recent past. The only previous Indian study conducted by the Indian Council of Medical Research (ICMR) included GDD, but studied only older children with mental retardation.[8] This ICMR multicentre study examined the genetic causes of mental retardation.

In our study, most (65%) of the children enrolled were <2 years of age with a mean age at presentation of 23.6 months, which is higher than the mean age of 0.7 years reported by Shevell *et al*. in their similarly designed study.[9] This is probably because of the referral nature of our institution, as is evident by a mean delay of

TABLE IV. Clinical features and aetiological determination (bivariate analysis)

Variable (*n*)		Aetiology determined (%)		p value	Odds ratio (95% CI)
		Yes	No		
Sex	Female (33)	76	24	0.663	—
	Male (67)	72	28		
Historical features	Yes (63)	73	27	0.996	1.00 (0.40–2.50)
	No (37)	69	31		
Birth asphyxia	Positive (20)	85	15	0.743*	2.42 (0.65–9.00)
	Negative (80)	70	30		
Sepsis	Positive (5)	80	20	0.590*	1.50 (0.16–14.1)
	Negative (95)	73	27		
Seizures	Positive (14)	79	21	0.443*	1.41 (0.37–5.53)
	Negative (86)	72	28		
Family history	Positive (19)	58	42	0.090	0.42 (0.15–1.12)
	Negative (81)	76	24		
Autistic features	Positive (6)	17	83	0.005*	0.06 (0.006–0.5)
	Negative (94)	77	23		
Head circumference	Abnormal (36)	83	17	0.081	2.44 (0.88–6.77)
	Normal (64)	67	33		
Specific dysmorphism	Positive (44)	77	23	0.394	1.48 (0.60–3.67)
	Negative (56)	70	30		
Neurological examination	Normal (51)	59	41	0.003*	5.01 (1.8–13.9)
	Increased tone (29)	83	17		
	Decreased tone (20)	95	5		
Physical findings	Abnormal (78)	77	23	0.090	2.30 (0.84–6.27)
	Normal (22)	59	41		
Severity of delay	Mild (25)	72	28	0.636	—
	Moderate (42)	69	31		
	Severe (33)	78	21		

* Fisher exact test

TABLE V. Aetiological profile of developmental delay/mental retardation

Study	*n*	Age group (year)	Aetiological yield (%)	HIE (%)	Cerebral dysgenesis (%)	Toxin exposure (%)	Chromosomal (%)	Syndromic (%)	Metabolic (%)	Others (%)
ICMR (1991)[8]	1314	All ages	40.3	—	—	—	23.7	11.5	4.9	—
Majnemer *et al.* (1995)[1]	60	All ages	63.3	10	17	8.3	10	3.3	5	10
Curry *et al.* (1997)[7]	—	All ages	50–70	—	7–17	5–13	4–28	53	1–5	3–15
Battalgia *et al.* (1999)[2]	120	2–19	81	3	4	1	15	3—7	3	2
Shevell *et al.* (2000)[9]	99	<5	44	9	10	9	6	2	—	7
van Karnebeek *et al.* (2005)[6]	281	0–17.9	50	0.7	—	6	20.06	55.3	4.6	5.3 (Molecular)
Srour *et al.* (2006)[12]	261	<5	40	22	16	7	24 (Both chromosomal and syndromic)	—	—	11 (Psychosocial)
Our study	100	0.5–5	73	15	11	1	20	14	4	8

HIE hypoxic–ischaemic encephalopathy

18.2 months between suspicion of GDD and presentation to us. The male preponderance is probably a reflection of sociocultural factors.

An aetiological diagnosis was made in 73% of children in this cohort. This is higher than in most studies from the 1980s, probably because of substantial advances in cytogenetics, dysmorphology, molecular genetics and imaging modalities. The spectrum of conditions seen in this study was similar to that in previous studies apart from certain minor differences (Table V). Four diagnostic categories (cerebral dysgenesis, chromosomal disorders including Down syndrome, HIE and multiple malformation syndromes) accounted for most of the aetiological diagnoses. In other studies, the variation in frequency of different diagnostic categories could be due to implementation of a screening programme for hypothyroidism and certain metabolic disorders such as phenylketonuria,[9] nature of the referred specialty, different clinical setting, selection criteria (institutionalized children with severe mental retardation),[7,10] or differences in diagnostic protocols. These studies vary with regard to the severity of retardation, selection of cases and age distribution, making comparison difficult.[7] Moreover, children with HIE, Down syndrome and hypothyroidism were excluded in most previous studies.

In our study, the contribution of HIE is higher than the 9%–10% reported by Majnemar and Shevell,[1] and Shevell *et al*.[9] Cerebral dysgenesis accounted for 11% of our study population, which is comparable to the 10%–17% incidence in other studies, reflecting advances in neuroimaging.[1,9] The importance of this lies in the fact that the risk of recurrence of these disorders has been reported to be extremely low.[10] The incidence of chromosomal anomalies including Down syndrome among the study population was 20%, which is comparable to that in previous studies.[2,6–8] Multiple malformation syndromes were present in 14% of the study population, higher than the reported 5% in studies by Majnemar and Shevell,[1] and Shevell *et al*.[9] but much less than in other recent studies.[6] This may also be explained by the increasing awareness that developmental/genetic factors underlie most cases of developmental delay and the knowledge that more and more developmentally delayed children may have a syndrome.[2] Exposure to toxins was underrepresented in our study, with only 1 child having foetal valproate syndrome. This may be explained by sociocultural factors and lack of availability of medical records with most families. Metabolic disorders were present in 4%, a figure similar to that found in most previous studies.[1,7,9,10] Hypothyroidism, a treatable cause, was present in 3% of children, an aetiology that is not seen in most western studies because of screening programmes in those countries. This emphasizes the need for thyroid profile testing in all children with idiopathic GDD in the absence of a universal screening programme for thyroid disorders in developing countries.

An important outcome of our study is that the percentage aetiological yield was constant across all categories of developmental delay, implying that an extensive search for aetiology should be done in all categories of developmental delay. This is in contrast to previous assumptions that severe developmental delay is more likely to have an organic cause.[2,9,12]

This study permitted the identification of successful predictors of aetiology on detailed history and examination. These included seizures, sepsis, birth asphyxia, microcephaly, features of dysmorphism and positive neurological findings. Absence of autistic features was more likely to yield an aetiology. Statistical significance was achieved only for absence of autistic features and positive neurological findings. The negative aetiological yield of autistic features needs to be highlighted, as it is not consistent with the recent work of other clinical investigators who have been searching for aetiological correlates of autism and pervasive developmental disorders.[11] A recent study showed an overall aetiological yield of 40%–55% in the absence of any coexisting autistic features.[12]

Thus, based on history alone we cannot decide whether further investigations would be worthwhile. This is in contrast to the study by Shevell *et al.* where positive historical features were more likely to yield an aetiology.[9] The positive predictive value of abnormal neurological examination and the negative predictive value of autistic features in that study are consistent with those in this study.

There is a controversy surrounding the potential diagnostic yield of various investigations, especially neuroimaging and cytogenetic studies. In our study, 53% had abnormal neuroimaging findings of which 33% were specific. This is significantly higher than in previous studies.[13] This may be an under-representation as MRI was not done in all cases. This is consistent with previous studies which reveal a high frequency of subtle markers (cavum septum pellucidum, mega cisterna magna and hypoplasia of the corpus callosum) of cerebral dysgenesis in MRI studies of mentally retarded subjects.[1] Thus, the earlier recommendation that neuroimaging was not necessary except in those with 'substantial impairments' probably does not hold true.[11]

In our study, MRI was superior to CT in detecting disorders such as migration defects though the numbers were too small for a recommendation to be made. However, CT alone was able to pick up most of the abnormalities, so that in the presence of cost constraints and lack of availability, CT can provide a reasonable yield. These findings are consistent with the recommendations of a consensus conference on evaluation of children with mental retardation.[7]

Karyotyping results suggest the utility of chromosome analysis in children with developmental delay, even in the absence of major malformations. However, in the presence of limited availability, testing can be restricted to children with developmental delay associated with dysmorphism and multiple malformations. With advances in molecular cytogenetic techniques such as fluorescent *in situ* hybridization (FISH), quantitative fluorescent polymerase chain reaction (QF-PCR), multiplex ligation-dependent probe amplification (MLPA) and array comparative genomic hybridization (CGH) and their use in children with unexplained developmental delay or mental retardation, the diagnostic yield has increased further.[14–20]

Additional laboratory investigations contributed to the diagnosis in 73% of children, while in 23% they were the sole means of arriving at a diagnosis. Earlier studies have also emphasized the importance of extensive investigations in children with developmental delay.[2]

Our study had certain limitations such as non-availability of MRI for all patients because of cost constraints, resulting in under-representation of the group with cerebral dysgenesis. Second, as many children in our study were drawn from the Genetics clinic, there was probably an over-representation of multiple malformation syndromes. Similarly, because of the referral nature of our institution, more children had severe developmental delay. However, this is unlikely to have altered our results, as we discovered no difference in the aetiological yield with severity of delay. Another important limitation was the non-availability of subtelomeric chromosomal rearrangement studies for our patients. This can detect 6.5%–7.4% of cases with moderate-to-severe mental retardation and 1.1% of cases with mild mental retardation.[21] Last but not least was the non-availability of advanced molecular techniques as mentioned above for routine diagnostic purposes.

In conclusion, our study reiterates that a thorough investigational approach is justified in children with GDD regardless of the severity of delay or absence of findings on history and physical examination.

REFERENCES

1 Majnemer A, Shevell MI. Diagnostic yield of the neurologic assessment of the developmentally delayed child. *J Pediatr* 1995;**127:**193–9.

2 Battaglia A, Bianchini E, Carey JC. Diagnostic yield of the comprehensive assessment of developmental delay/mental retardation in an institute of child neuropsychiatry. *Am J Med Genet* 1999;**82:**60–6.

3 Palfrey JS, Frazer CH. Determining the etiology of developmental delay in very young children: What if we had a common internationally accepted protocol? *J Pediatr* 2000;**136:**569–70.

4 Van Buggenhout GJCM, Trommelen JCM, Brunner HG, Hamel BCJ, Fryns JP. Clinical etiological survey of a population of 471 mentally retarded patients living in an institution in the southern part of The Netherlands. *Community Genet* 2001;**4:** 109–22.

5 Shevell M, Ashwal S, Donley D, Flint J, Gingold M, Hirtz D, *et al*., Quality Standards Subcommittee of the American Academy of Neurology; Practice Committee of the Child Neurology Society. Practice parameter: Evaluation of the child with global developmental delay: Report of the Quality Standards Subcommittee of the American Academy of Neurology and The Practice Committee of the Child Neurology Society. *Neurology* 2003;**60:**367–80.

6 van Karnebeek CD, Jansweijer MC, Leenders AG, Offringa M, Hennekam RC. Diagnostic investigations in individuals with mental retardation: A systematic literature review of their usefulness. *Eur J Hum Genet* 2005;**13:**6–25.
7 Curry CJ, Stevenson RE, Aughton D, Byrne J, Carey JC, Cassidy S, *et al*. Evaluation of mental retardation: Recommendations of a Consensus Conference: American College of Medical Genetics. *Am J Med Genet* 1997;**72:**468–77.
8 Multicentric study on genetic causes of mental retardation in India. ICMR Collaborating Centres and Central Co-ordinating Unit. *Indian J Med Res* 1991;**94:**161–9.
9 Shevell MI, Majnemer A, Rosenbaum P, Abrahamowicz M. Etiologic yield of subspecialists' evaluation of young children with global developmental delay. *J Pediatr* 2000;**136:**593–8.
10 Schaefer GB, Bodensteiner JB. Evaluation of the child with idiopathic mental retardation. *Pediatr Clin North Am* 1992;**39:**929–43.
11 First LR, Palfrey JS. The infant or young child with developmental delay. *N Engl J Med* 1994;**330:**478–83.
12 Srour M, Mazer B, Shevell MI. Analysis of clinical features predicting etiologic yield in the assessment of global developmental delay. *Pediatrics* 2006;**118:**139–45.
13 Lingam S, Read S, Holland IM, Wilson J, Brett EM, Hoare RD. Value of computerised tomography in children with non-specific mental subnormality. *Arch Dis Child* 1982;**57:**381–3.
14 Harada N, Hatchwell E, Okamoto N, Tsukahara M, Kurosawa K, Kawame H, *et al*. Subtelomere specific microarray based comparative genomic hybridisation: A rapid detection system for cryptic rearrangements in idiopathic mental retardation. *J Med Genet* 2004; **41:**130–6.
15 Shaw-Smith C, Redon R, Rickman L, Rio M, Willatt L, Fiegler H, *et al*. Microarray based comparative genomic hybridisation (array-CGH) detects submicroscopic chromosomal deletions and duplications in patients with learning disability/mental retardation and dysmorphic features. *J Med Genet* 2004;**41:**241–8.
16 Anderlid BM, Schoumans J, Annerén G, Sahlén S, Kyllerman M, Vujic M, *et al*. Subtelomeric rearrangements detected in patients with idiopathic mental retardation. *Am J Med Genet* 2002;**107:**275–84.
17 Rooms L, Reyniers E, van Luijk R, Scheers S, Wauters J, Kooy RF. Screening for subtelomeric rearrangements using genetic markers in 70 patients with unexplained mental retardation. *Ann Genet* 2004;**47:**53–9.
18 Kok K, Dijkhuizen T, Swart YE, Zorgdrager H, van der Vlies P, Fehrmann R, *et al*. Application of a comprehensive subtelomere array in clinical diagnosis of mental retardation. *Eur J Med Genet* 2005;**48:**250–62.
19 Schoumans J, Ruivenkamp C, Holmberg E, Kyllerman M, Anderlid BM, Nordenskjöld M. Detection of chromosomal imbalances in children with idiopathic mental retardation by array based comparative genomic hybridisation (array-CGH). *J Med Genet* 2005;**42:**699–705.
20 Monfort S, Orellana C, Oltra S, Roselló M, Guitart M, Martínez F. Evaluation of MLPA for the detection of cryptic subtelomeric rearrangements. *J Lab Clin Med* 2006;**147:**295–300.
21 Battaglia A, Carey JC. Diagnostic evaluation of developmental delay/mental retardation: An overview. *Am J Med Genet* 2003;**117C:**3–14.

Obituaries

Many doctors in India practise medicine in difficult areas under trying circumstances and resist the attraction of better prospects in western countries and in the Middle East. They die without their contributions to our country being acknowledged.

The National Medical Journal of India wishes to recognize the efforts of these doctors. We invite short accounts of the life and work of a recently deceased colleague by a friend, student or relative. The account in about 500 to 1000 words should describe his or her education and training and highlight the achievements as well as disappointments. A photograph should accompany the obituary.

—Editor