Guillain-Barré Syndrome with Acute Lymphoblastic Leukemia

Binitha Rajeswari, *Syam Krishnan, *C Sarada, and Parukuttyamma Kusumakumary

*From Division of Pediatric Oncology, Regional Cancer Centre; and *Department of Neurology, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthapuram, India.*

Correspondence to:
Dr Binitha Rajeswari, Lecturer, Division of Pediatric Oncology, Regional Cancer Centre, Thiruvananthapuram, Kerala 695 011, India. rbinitha@yahoo.co.in
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Guillain-Barré syndrome (GBS) is rarely reported in children with acute lymphoblastic leukemia and may be difficult to differentiate from vincristine induced neuropathy. We report two children with acute lymphoblastic leukemia on induction chemotherapy who developed GBS. The diagnostic issues and potential pathogenic mechanisms underlying GBS in pediatric patients with ALL are discussed.

Keywords: *Acute Lymphoblastic Leukemia, Chemotherapy, Guillain-Barré Syndrome, Vincristine.*

There is substantial evidence for autoimmune cause for Guillain-Barré syndrome (GBS), the most frequent cause of acute flaccid paralysis [1]. GBS has been reported in association with hematologic malignancies like non-Hodgkin lymphoma, chronic lymphocytic leukemia and acute lymphoblastic leukemia (ALL) in adults. There are only few reports of GBS in children with ALL [2,3]. Differentiation from other neuropathies is important from the therapeutic point of view [3,4]. We report two cases of GBS in children on induction chemotherapy for ALL and discuss the clinical and electrophysiological features and potential mechanisms of pathogenesis.

Case Report

Case 1: A 6-year-old boy was evaluated for fever, pallor, cervical lymphadenopathy and hepatosplenomegaly. Bone marrow aspiration and flow cytometry was suggestive of T-cell acute lymphoblastic leukemia. His CSF did not show blasts. He was started on induction chemotherapy with prednisolone, vincristine, daunorubicin and L-asparaginase. In the fifth week, he developed symmetrical and gradually progressive proximal and distal weakness of upper and lower limbs, progsessing to dense quadriplegia over a period of 3 days. Weakness of facial muscles was noticed on third day. He did not have any sensory symptoms. The tendon reflexes were depressed initially and totally disappeared by the third day.

Electrophysiological evaluation done on fourth day of illness was suggestive of a motor axonopathic polyradiculoneuropathy. The common peroneal nerves were bilaterally unexcitable. Stimulation of the tibial, median and ulnar nerves resulted in compound muscle action potentials (CMAPs) with marked reduction of amplitude bilaterally; conduction velocities were normal. F waves were not elicitable from peroneal nerves; F waves from other nerves showed prolonged latency. The sensory nerve action potentials (SNAPs) were normal from all the tested nerves. Correlating the clinical and electrophysiological findings, acute motor axonal neuropathy (AMAN) – a subtype of GBS was diagnosed. He was given a course of intravenous immunoglobulin (IVIg) (0.4 g/kg/day) for 5 days. CSF was re-examined on the eighth day which showed: glucose-55 mg/dL; protein-163 mg/dL; cell count-2 lymphoayties/mm^3. No blasts were detected in the CSF. The weakness began to improve on the third day of treatment with immunoglobulin. Eight weeks later, he had normal power of all the limbs and was ambulant normally. He is presently on chemotherapy.

Case 2: A 2-year-old boy was evaluated for fever, pallor and hepatosplenomegaly. Bone marrow flow cytometry was diagnostic of precursor B acute lymphoblastic leukemia with co-expression of CD 13 and CD33. His CSF did not show blasts. He was started on induction chemotherapy with prednisolone, vincristine, daunorubicin and L-asparaginase. In the third week of chemotherapy, he developed fever, cough and loose stools and was started on broad-spectrum antibiotics and antifungals. One week later, he developed rapidly progressive ascending areflexic weakness of the limbs; within 24 hours, he had paralysis of respiratory muscles necessitating emergency endotracheal intubation and mechanical ventilation. His nerve conduction study showed marked reduction of CMAPs from all upper and lower limb nerves tested. None of the F waves was elicitable. Conduction velocities and distal motor latencies were relatively preserved. All the SNAPs

were elicited normally. Repetitive nerve stimulation from ulnar and facial nerves did not result in any decremental response. He was started on IVIg and he showed signs of improvement in the form of voluntary movements of the limbs, on the fourth day. However, he succumbed to sepsis.

Neither of the children had any known family history of hereditary neuropathies or foot deformity. The parents were evaluated retrospectively for evidence of hereditary neuropathies and they were normal.

DISCUSSION

We report two patients who developed GBS during treatment for ALL. The pattern and evolution of the neurological syndrome and electrodiagnostic features in both children were consistent with AMAN variant of GBS [5]. The CSF study was supportive of the diagnosis in the first child but could not be repeated after the onset of polyneuropathy in the second case because of severe thrombocytopenia and coagulopathy.

Guillain-Barre syndrome is an acute immune polyneuropathy and demyelinating and axonal subtypes are described [1]. There are only very few reports of GBS in children with ALL [2,3,6]. Out of the five cases so far reported, three were from a single centre [3]. Autoimmune disorders are known to occur in ALL [7,8]. Depletion of the regulatory T cells which suppress auto-reactive T cells, either resulting from ALL or intensive chemotherapy has been postulated as the mechanism underlying immune thrombocytopenia in ALL[7]; similar mechanisms may underlie the genesis of acute immune neuropathies in ALL. The immunological vulnerability of the peripheral nervous system could be increased in lymphoproliferative disorders; known infective triggers could precipitate an immune neuropathy in this setting. The association between GBS and ALL could be coincidental or causal. However, the occurrence of immune neuropathy in immunocompromised children is interesting. Improvement of GBS with immunotherapy (before remission of ALL) is not unexpected as GBS is an autoimmune disorder, not directly related to the hematologic malignancy.

An important consideration in children with ALL developing neuropathy while on chemotherapy is vincristine-induced neuropathy. But the clinical and electrodiagnostic findings will be distinct for vincristine induced neuropathy, [9] which is a toxic, "dying-back" neuropathy with prominent sensory involvement [10]. Vincristine may also cause a fulminant neuropathy with severe weakness in patients with Charcot-Marie-Tooth disease; the clinical and electrophysiological features in our cases were not supportive of this. Critical illness polyneuropathy could be considered in critically ill ALL patients; however, our patients did not satisfy the definition for "critical illness" (no multi-organ failures / mechanical ventilation) prior to onset of neuro-muscular illness.

It has been recently suggested that GBS in ALL is probably more common than expected[3]; a high index of suspicion is needed for differentiation from other neuropathies. Electrophysiological studies guide to the correct diagnosis. The differentiation is important to initiate timely immunomodulatory therapies for GBS and avoid unnecessary withdrawal of vincristine, which could worsen the outcome of ALL.

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Atypical Hemolytic Uremic Syndrome with Membranoproliferative Glomerulonephritis

***KUMUD MEHTA, VAISHALI MORE, ARUN CHITALE AND SHAILA KHUBCHANDANI**

*From the *Department of Pediatric Nephrology, Jaslok Hospital and Research Center and Department of Pediatrics, Nephrology Division, Dr. D.Y.Patil Medical College, Hospital and Research Center, Nerul, Navi-Mumbai, Maharashtra, India.*

Correspondence to:
Dr Vaishali More, 201, M-5, C-wing, Palm Acres CHS, Pratiksha Nagar, Sion, Mumbai 400 022, India, morevaishali28@gmail.com
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Atypical hemolytic uremic syndrome (aHUS) associated with membranoproliferative glomerulonephritis (MPGN) is an uncommon clinical presentation, especially in children. We report a 8-year-old-boy who presented like aHUS but the kidney biopsy showed MPGN type 1.

Keywords: *Atypical hemolytic uremic syndrome, Hypocomplementemia, Membranoproliferative glomerulonephritis.*

Atypical hemolytic uremic syndrome (aHUS) and membranoproloiferative glomerulonephritis (MPGN) are uncommon diseases. Both these conditions are widely studied and reported to be associated [1,2]. Previously they were considered to be chance association but now there are reports of the role of factor H in the etiopathogenesis of MPGN and aHUS.

CASE REPORT

An 8-year-old boy was brought with the complaints of decreased urine output, generalized edema and fever since one week. He had no history of similar episodes in the past or history suggestive of chronic kidney disease in the family. There was no history of diarrhea, sore throat, rash or hematuria preceding this illness. Examination revealed anasarca, periorbital puffiness and pallor. Patient did not have rash, joint involvement or purpura. Blood pressure was normal. He had abdominal distension due to ascites. Liver was tender and palpable 4 cm below the subcostal margin with a span of 10 cm. Spleen was not palpable.

Investigations on admission, revealed hemoglobin level of 4.6 g/dL, reticulocyte count of 2%, leukocyte count of 12,200/cu mm with 67% neutrophils, 25% lymphocytes and platelets 1,72,000/cu mm. Peripheral smear showed microcytosis, anisocytosis, schistocytes, few tear drop and target cells. Blood level of albumin was 3.1 g/dL, total proteins 5.6 g/dL, pH 7.4, pCO_2 26 mm Hg and bicarbonate 16.1 mEq/L, creatinine 1.2 mg /dL, urea nitrogen 65 mg/dL, sodium 136 mEq/L and potassium 5.7 mEq/L. Antistreptolysin O (ASO) was negative, C3 was 28 mg/dL and hepatitis B and C serology were negative. Urinalysis showed 3+ proteinuria, 10-15 red cells /hpf and 5-10 leukocytes/hpf. Prothrombin time was 17 seconds (control 19 seconds) and aPTT was 27 seconds. Lactate dehydrogenase and D-dimer were 772 IU/L and 2000 ng/dL, respectively. Serum C4 was normal and antinuclear antibodies anti-ds, DNA were negative. A diagnosis of acute renal failure with microangiopathic hemolytic anemia due to HUS was made. There was a steady increase in blood urea, creatinine and potassium with a fall in urine output over the next two days. Peritoneal dialysis was done for 72 hours following which these levels normalized and the urine output improved.

Renal histology showed ten enlarged glomeruli with diffusely thick basement membrane, proliferation of mesangial cells, fewer endothelial cells and neutrophil infiltration. The loops were obliterated. The tubules showed focal necrosis, hydrophobic changes and atrophy. The vessels showed mild luminal narrowing due to myointimal thickening. The interstitium revealed few lymphocytes. Immunofluorescence revealed deposition of IgM, C_3 and C1q in the mesangium and capillary loops. IgG and IgA were negative. Electron microscopy revealed proliferation of endothelial and mesangial cells. The lamina densa showed excess of basement membrane material with zones of interpositioning and subendothelial electron dense deposits. The foot processes were flat. The findings were suggestive of membranoproloiferative glomerulonephritis (MPGN) type 1.

The patient was treated with oral prednisolone at a dose of 2 mg/kg/day and fresh frozen plasma for the first few days followed by alternate day transfusions to which patient responded well. These were then tapered and stopped when the activity of HUS decreased. During the course of prednisolone therapy, blood pressure increased requiring multiple agents. Urine albumin reduced, but 5 months later showed significant albuminuria. Therapy with mycophenolate mofetil resulted in decrease in proteinuria.

Two months later, he was admitted with fever, vomiting, diarrhea and abdominal pain and 4+ proteinuria. He rapidly developed septicemia with hypotension and multiorgan failure, and died after four days of intensive care and ventilator support.

DISCUSSION

HUS with MPGN has been widely studied and reported in the past [1,3]. The earliest reports just mention it as a chance association or as HUS secondary to MPGN whereas, recent reports implicate the role of factor H which is an important component of the alternate complement pathway in both HUS as well as MPGN [1,2]. Ten percent of HUS patients are due to atypical form which is distinct and different from the typical HUS. The atypical form of HUS has a poor prognosis and terminal renal insufficiency occurs in over 50% with death rates close to 25% [3].

Our patient had a clinical presentation of aHUS on admission and his renal biopsy was suggestive of MPGN type I. There was no evidence of HUS on the biopsy findings, yet the patient responded well to plasma infusions. The co-existence of HUS with MPGN can be explained on the basis of factor H deficiency.

Mutations in the factor H gene are associated with severe and diverse diseases including the rare renal disorders of HUS and MPGN, and and the more frequent age related macular degeneration [4-6]. In a study on 19 patients of glomerulonephritis with C3 deposits, assays were performed for factor H, factor I and membrane cofactor protein to determine whether they share a common genetic susceptibility. The study suggested that dysregulation of the complement alternative pathway is probably associated with a wide spectrum of diseases ranging from HUS to MPGN with C3 deposits [6]. The clinical clue to the diagnosis of MPGN in this case was persistent low C3 complement, which is found only in factor H deficient or complement associated HUS. In a study of 16 factor H-deficient patients, six had a homozygous deficiency of which four presented with MPGN and two had aHUS. Patients with heterozygous mutations in factor H gene are also reported to develop aHUS [7].

Treatment options include control of hypertension, plasma infusions or plasmapheresis and use of steroids, which will help in control of MPGN as well as a HUS. Eculizimab has also been used in the treatment of refractory MPGN [8] and has been found useful in patients where mycophenolate mofetil does not result in a satisfactory response.

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3p Deletion Syndrome

ANUPAM KAUR AND *S KHETARPAL
*From the Department of Human Genetics, Guru Nanak Dev University; and , *39-C, Circular Road; Amritsar, Punjab, India.*

Correspondence to:
Dr Anupam Kaur, Reader, Human Genetics, Guru Nanak Dev University
Amritsar, Punjab 143 005, India.
anupamkaur@yahoo.co.in
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3p deletion is a rare cytogenetic finding. Here we describe a 3 months old male with congenital malformations. His karyotype revealed 3p deletion 46,XY,del(3)(p25-pter). The child had flexion deformity of wrist and elbow which has never been reported before.

Keywords: *3p deletion, trignocephaly, micrognathia.*

The 3p deletion syndrome has been proposed as a contiguous gene syndrome with the spectrum of defects depending upon the overall size of the deleted segment [1]. The phenotype of individuals with 3p deletions varies from normal to severe. The 3p25 chromosome deletion syndrome was first reported in 1978 [2]. Since the first case, less than 50 cases with distal 3p deletions have been reported. Characteristic features of the syndrome include low birth weight, microcephaly, trigonocephaly, hypotonia, mental and growth retardation, ptosis and micrognathia. Other features that may be seen include polydactyly, renal anomalies, congenital heart defects, ear anomalies, and gastrointestinal tract anomalies. It has been suggested that a 1.5 Mb minimal terminal deletion including the two genes *CRBN* and *CNTN4* in chromosome 3 are sufficient to cause the syndrome. In addition the *CHL1* gene, mapping at 3p26.3 distally to *CRBN* and *CNTN4*, was proposed as candidate gene for a non specific mental retardation because of its high level of expression in the brain [3].

CASE REPORT

A 3-months-old male child with congenital malformations was referred to us for cytogenetic investigations. Detailed pedigree analysis and in-depth evaluation of the clinical reports was undertaken. Chromosome preparations were made from peripheral lymphocytes using RPMI 1640 medium and phytohemagglutinin using standard method with modifications [4] and G-banding was done. Fifty metaphases were examined for numerical as well as structural abnormalities and five metaphases were karyotyped with Applied Imaging Software (Cytovision). A written consent was obtained from the parents before all the investigations.

A full term male child, weighing 2.10 kg born by caesarian section was presented with multiple congenital anomalies. The proband was the first child of healthy, non-consanguineous parents. The mother had an uneventful pregnancy. He had a delayed and weak cry. At the time of examination, the infant was 3 months old with triangular face, hypertrichosis, bilateral exophthalmous eyeballs, depressed nasal bridge with wide nostrils, retrognathia and high arched palate. He presented bilateral flexion deformity of wrist and elbow, and calceneovalgus deformity of right foot. He was lethargic, his neurological and motor milestones were delayed. He had history of neonatal asphyxia, cyanotic spells, recurrent vomiting and sleep apnea. *X*-ray skull showed partial closure of sutures. The CT scan revealed anteriorly pointed frontal closure of the metopic suture suggesting craniosynostosis with trignocephaly. The venous sinuses were prominent and hyperdense. Routine peripheral blood film showed normochromic picture. Karyotyping of the case showed terminal deletion of the chromosome 3. The child expired a week after presentation.

DISCUSSION

3p deletion syndrome is a rare disorder involving the short arm of chromosome 3. The clinical findings of our case were very severe and similar to the description in literature. The flexion deformity has previously not been reported in the literature. Karyotyping of the present case showed 46, XY, del(3)(p25-p26.34). Parents were not available for further investigations. This syndrome presents a strong connection between the severity of the disease and the portion of the deletion. Despite investigations of several genes in the 3p region involved in CNS development, a causative relationship between any particular transcript and the range of observed clinical manifestations has remained elusive. The minimal candidate region for 3p deletion, implicates haploinsufficiency of various genes and demonstrates the utility of high-resolution investigations of rare chromosomal rearrangements [6]. Some of the known genes in the 3p" phenotype have been previously described [1,5-10].

Karyotyping remains the gold standard for detecting chromosomal aberrations in cases with congenital anomalies. A meaningful correlation between the deletion and the clinical phenotype is not possible until further use of high-resolution investigations like CGH array to fully characterize the case, which was not possible due to financial constraints.

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Thoracoscopic Ligation of Thoracic Duct for Spontaneous Chylothorax

ARVIND KUMAR, BELAL BIN ASAF, *KRISHAN CHUGH AND *NEETU TALWAR
*From Centre for Chest Surgery and Lung Transplantation, Institute of Robotic Surgery, and *Institute of Child Health; Sir Ganga Ram Hospital, New Delhi.*

Correspondence to:
Prof. Arvind Kumar, Room No. 2328, Institute of Robotic Surgery, Sir Ganga Ram Hospital, New Delhi, India.
arvindreena@gmail.com
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Spontaneous chylothorax, without a predisposing factor is an uncommon cause of pleural effusion beyond the neonatal period. We present a case of left sided spontaneous chylothorax in a 20-month-old boy. We report successful management of this difficult problem with thoracoscopic ligation of thoracic duct after a failed trial with conservative management.

Keywords: *Chylothorax, Thoracoscopy, Thoracic duct, VATS.*

Chylothorax has various causes, including malignancy, trauma (including surgery), and miscellaneous disorders (such as deep vein thrombosis, sarcoidosis, and congestive heart failure), and can also be idiopathic [1,2]. Undetected malformations of the lymphatic trunks are implicated as a cause of spontaneous chyle accumulation. Management of spontaneous chyle accumulation in a child is a challenging task. We present a child with left sided spontaneous chylothorax who was managed with thoracoscopic ligation of thoracic duct on right side.

CASE REPORT

A 20-month-old boy presented with fever and breathing difficulty for one week. There was no history of trauma or operative intervention in the child. The mother gave no history of excessive cough or vomiting. The child was otherwise healthy, with no significant past medical history. There was no history of recent trauma or history suggestive of cardiopulmonary disease. The child's immunization was up to date.

On examination, the child weighed 12 kg, was febrile,

pulse rate was 130/ minute, blood pressure was 90/64 mm Hg and respiratory rate was 56/minute. His blood biochemistry and hematological parameters (total leucocyte count was 9600 with 80 % neutrophils, 12% lymphocytes, 7% monocytes and 1% eosinophils) were all within normal limits. The CRP level was 1.8 mg/L and ESR was 4 mm. Chest examination revealed absent breath sound on left side. Chest *X*-ray revealed an opaque left hemithorax. Computed tomography of chest showed massive left sided pleural effusion with mediastinum shifted to right side.There was no mass or any other abnormality. Left side intercostal drain (24 Fr) was inserted and 640 mL milky fluid was drained from the chest. Fluid analysis revealed total cell count of 10600 per cubic mm with lymphocytic predominance, and high triglyceride (150 mg/dL). He was started on intravenous antibiotics and octreotide infusion at 240 µg/day in 12 cc NS at the rate of 0.5 mL/h for 7 days. He became afebrile with the treatment but chest tube continued to drain 600-700 mL of milky fluid every day. Lymphoscintigraphy performed after 5 days of conservative approach showed a large leak of dye in left pleural space; however, the site of leak could not be identified. The chest tube output and character remained unchanged despite starting the child on fat restricted diet. Subsequently, oral feeds were stopped and total parenteral nutrition (TPN) was started; octreotide was continued for further two weeks. The chest tube output reduced to 400 mL/day of rice water color fluid in the first few days and remained unchanged thereafter. A surgical consultation was sought when conservative treatment failed even after 3 weeks. At this stage, thoracoscopic ligation of thoracic duct on right side was offered.

The procedure was performed under general anesthesia. Selective deflation of right lower lobe was achieved using Fogarty balloon tipped catheter inserted through the ETT and advanced to the right lower lobe bronchus under fiber optic bronchoscope guidance. The child was placed supine with 30 degrees right up position. Three 5-mm ports were used: the port positions included the mid-axillary line 5th intercostal space, mid clavicular line 7th intercostal space, and posterior axillary line 7th intercostal space. The procedure was begun with incision of mediastinal pleura between azygous vein and thoracic aorta in the lower chest (just above the diaphragm). The thoracic duct was identified as a thin walled tubular structure lying between the azygous vein and the aorta. Butter milk was given to the child through nasogastric (Ryle's) tube to make the duct prominent for visualization. Metallic clips were applied to occlude the duct. The milky output through the left chest tube stopped immediately after clipping of the duct and the closure done after insertion of 20 Fr chest tube into right chest. The child tolerated the procedure well, was extubated on the table and allowed orally from the next day. The right chest tube drained 100 mL of serosanguineous fluid on the first post-operative day. It was removed on the second post-operative day when the drainage was 40 mL. Despite normal food intake, the left chest tube output started reducing with each passing day, stopping completely on day 14 and the tube was removed on day 16. The child was discharged the next day. He has been on normal diet and is doing well at 6-months follow up.

DISCUSSION

Chylothorax needs prompt treatment. Drainage of the pleural cavity by chest-tube relieves the patient of breathing difficulty. Thereafter, conservative treatment should be started, consisting of restriction of dietary fat to medium-chain triglyceride and fluid and electrolyte replacement. If there is no improvement, all oral intakes should be stopped and total parenteral nutrition should be implemented [2-4]. Although, there is no uniform agreement in medical literature, several authors have reported successful treatment of cases of congenital and postoperative chylothorax in children with octreotide infusion [4,5]. TPN has its own attendant complication and it is a challenging task to keep a 20-month-old child nil orally for a long time.

If loss of chyle persists, surgical treatment should be considered. Pleurodesis with talc or povidone-iodine, fluoroscopically guided embolization of the thoracic duct, pleuro-peritoneal shunt and pleurectomy have been tried with variable success. Surgical ligation of the thoracic duct represents the most definitive treatment of chylothorax. There are a very few reports of use of thoracoscopic thoracic duct ligation for spontaneous chylothorax in a child in the English literature. We could find only two reports describing the successful thoracoscopic ligation in such circumstances [6,7]. Martinez, *et al*. [7] subsequently published an erratum stating that there case report was not idiopathic but probably secondary to trauma [7]. In its course through the left chest, the thoracic duct is quite inaccessible. Hence it is accessed and ligated in the right lower chest, which takes care of left side leaks also. Some of these patients, however, do drain the chylous fluid, for few days, from the thoracic duct segment distal to the site of ligation, which closes in a few days. Traditionally, thoracic duct ligation in the right chest has been done by thoracotomy. Now, with the advancement of minimal access techniques, the same is possible through thoracoscopic approach, providing the benefits of minimal access surgery. Ample evidence in the literature

has proved the effectiveness of thoracoscopic ligation of thoracic duct in the management of chylothorax [8,9]. After thoracoscopic thoracic duct ligation, the output in our patient dropped to half of the usual output in the immediate postoperative period and decreased slowly over next few days to stop completely in 14 days. This was either due to leakage from the segment distal to the site of ligation (which healed slowly) or due to an accessory duct leaking into left pleural cavity.

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Is INH Waging a Lonely Losing Battle

The Updated National Guidelines for Pediatric Tuberculosis in India, 2012, [1] has rightly emphasized, at length, the need for becoming more aggressive in our treatment of pediatric tuberculosis (dropping out 3 drugs from all regimens *i.e*. HRZ). The area of chemoprophylaxis, however, has been left untouched [except for raising the dose of INH to 10 mg/kg/day). We all know and accept that resistance to first line AKT is rapidly emerging and the article itself acknowledges that " the drug Category III has been withdrawn in view of high INH resistance [>5%] in our community". I am sure that there is a lurking fear that this figure may be much higher. In such a setting, are we justified in offering a single drug as prophylaxis? Many years ago, I had suggested that INH may not be enough for prophylaxis [2]. Today I strongly feel that this is an idea whose time has come. Serious thought needs to be given to the case of adding a second drug so that no contact is exposed to a bacillus which is resistant to the drug he is using, thus negating any benefit to him. This scenario also exposes the contact to the risk of developing tuberculous disease and it's complications.

MUKESH SANKLECHA AND S SUNDARESAN
Bombay Hospital Institute of Medical Sciences, Mumbai, India.
doctormukesh@gmail.com

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Substance Abuse in Urban School Going Adolescents in India: A Growing Challenge

The epidemic of substance abuse in the young has assumed alarming dimensions in India. Changing cultural values, increasing economic stress and dwindling supportive bonds are contributing factors.The Global Youth Tobacco Survey (GYTS) showed 3.8% children to be smokers and 11.9% using smokeless tobacco [1]. Most studies in India were done on the lower socioeconomic section such as the survey by Bansal, *et al*. [2], which showed 45% street children using varied substances. Most previous studies demonstrate alcohol as the commonest substance used (60-98%) followed by cannabis (4-20%) [3].

We conducted a survey among adolescents aged 12-16 years studying in high school in three prominent urban schools in Bangalore. All participants (*n*=354) (56.7% females) whose parents consented were administered a questionnaire. Results are shown in ***Table* I**, The most common substances abused included alcohol (28%) and glue-sniffing (20.2%), with a near equal gender distribution. 15.4% reported a relative and 15.3% a peer as the first person to introduce them to the substance. The most common reason for using any substance was "curiosity" to try a new substance in 16.9% cases, "enjoyment" in 12.2% and "to be accepted by others" in 12%. Smoking and consumption of cannabis and cocaine was limited to boys only.

Contrary to the popular belief that smoking was the most common substance abused, we found prevalence of smoking to be quite low [4]. Hookah consumption was

TABLE I PROFILE OF SUBSTANCE ABUSE AMONG URBAN SCHOOL GOING ADOLESCENTS IN BANGALORE (N=354).

	Number (%) (years)	*Median age of start of consumption*	*Number of times consumed per wk (median)*
Smoking	12 (3.4)	15	2
Hookah	22 (6.2)	13	1
Alcohol	99 (28.2)	12	1
Glue-sniffing	71 (20.2)	11	3
Cannabis	2 (0.6)	11	1
Cocaine	3 (0.9)	12	2

tried and used by a significant number of adolescents. Inspite of a ban issued in Bangalore against Hookah cafes, they continue to thrive in the city and contribute to a huge number of children being addicted to the same. This; however, may not reflect the situation in other parts of India, as hookah consumption is closely linked to the availability and presence of joints in the vicinity. We also found 'sniffing' being high prevalent among urban adolescents. A previous review of all substance abuse in India has not reported this finding [5].

KR BHARATH KUMAR REDDY AND ASTHIK BISWAS
Department of Paediatrics,
Raju Multispeciality Hospital,
CMR Layout, Lingarajapuram,
Bangalore 560 084, Karnataka, India.
bharathreddykr@yahoo.co.in

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Updated National Guidelines for Pediatric Tuberculosis: Concerns Regarding Neurotuberculosis

I read with interest the recent Updated National guidelines for pediatric tuberculosis in India [1]. There are few important concerns in guidelines regarding neurotuberculosis which I wish to highlight.

First, there are discrepancies in dose ranges of isoniazid, rifampicin and pyrazinamide from the latest WHO guidelines and should be corrected. WHO currently recommends the following daily doses of antituberculosis medicines for the treatment of tuberculosis in children: isoniazid–10 mg/kg (range 10-15 mg/kg); rifampicin–15 mg/kg (range 10–20 mg/kg), pyrazinamide-35 mg/kg (30-40 mg/kg); ethambutol–20 mg/kg (15-25 mg/kg) [2]. It is important as upper end of the recommended dose range should be considered in neurotuberculosis in view of uncertain penetration of antituberculosis medicines into the central nervous system. The dose range suggested in published national guidelines probably follows WHO 2006 guidelines and should be corrected according to WHO 2009 guidelines. Second concern is regarding the duration of antitubercular therapy in neurotuberculosis. WHO recommends that duration of antitubercular therapy should be at least 12 months [3]. Similarly, a systemic review also identifies that there is no evidence base for shorter duration regime [4]. So, the recommendation of shorter 9 months duration is inappropriate and not evidence-based. Third, selection of third drug as ethambutol in continuation phase of previously treated cases has poor evidence-base with regard to neuro-tuberculosis. As pyrazinamide has better central nervous system penetration and bactericidal effect, it is probably a better choice as the third drug in continuation phase of previously treated cases.

Overall, I must congratulate authors for very comprehensive guideline and I hope the revised version would focus on the concerns regarding neuro-tuberculosis.

JITENDER KUMAR SAHU
Assistant Professor, Pediatric Neurology Division,
Department of Pediatrics,
Post Graduate Institute of Medical Education & Research,
Chandigarh, India. jsh2003@gmail.com

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REPLY

In response to letter from Sahu, we wish to inform that: (*a*) the group extensively deliberated about appropriate doses for anti-TB drugs to be recommended for our country based on available evidence and concluded that the earlier recommended dosages needed revision. The current dosages were arrived after looking into various available pharmacokinetic data and evidence within and outside the country (published and unpublished data from studies at AIIMS and NIRT). The group arrived at these recommendations as a consensus, while keeping in mind the absolute need for adequate serum levels and also the possible risk of cumulative hepatotoxicity; (*b*) the group recommends the total duration of ATT in intracranial TB including TB Meningitis should be 9-12 months depending upon the clinical progress on treatment. This is in consonance with available evidence and experience; and (*c*) among retreatment cases, the INH resistance is significant but not absolute, hence a third drug ethambutol, is added to in the continuation phase (RHE). There is no scientific basis or evidence for including pyrazinamide instead of ethambutol in the continuation phase. Pyrazinamide works best when there is active inflammation and in acidic pH, hence its benefit may not be seen during the continuation phase [1]. Furthermore, addition of Ethambutol not only helps in preventing emergence of drug resistance [2] but also would minimize the potential risk of hepato-toxicity with prolonged use of the suggested three hepatotoxic drugs (RHZ).

VARINDER SINGH AND BN SHARATH
4vsingh@gmail.com

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Updated National Guidelines for Pediatric Tuberculosis in India, 2012: Some Unresolved Issues

With respect to the recently published updated national guidelines for pediatric tuberculosis in India [1], we feel that the following issues need to be clarified for the benefit of practicing pediatricians.

1. Management algorithm (***Fig*.1a**) describes that sputum positive cases need not undergo a chest *X*-ray. While *X*-ray chest may not be necessary for diagnosis and initiation of treatment, it is vital for follow up and determination of duration of intensive phase treatment.
2. The guideline says that "There is no role for inaccurate/inconsistent diagnostics like serology (IgM, IgG, IgA antibodies against MTB antigens), various in-house or non-validated commercial PCR tests and BCG test." PCR is a very useful and promising diagnostic test for tuberculosis [2-4], though the existing commercial PCRs are non-validated. Since the PCRs for TB are likely to be validated in near future, it should have been mentioned separately rather than clubbing it with serological and BCG tests.
3. Management of childhood tuberculosis through DOTS centre is programmatically logical, but if a child has to attend DOTS centre three days a week, then his/her academic performance, self-esteem and mainstreaming is likely to be compromised. Therefore we need to find a practical solution to address this very important issue. DOTS providers are not highly skilled workers, hence one of the viable solutions could be to train school teachers assigned to 'medical room' in most of the schools and give them the responsibility of DOTS providers after initial registration at DOTS center. This could significantly minimize visits to DOTS centre.
4. The guidelines recommend INH prophylaxis to "All asymptomatic contacts (under 6 years of age) of a smear positive case, after ruling out active disease and irrespective of their BCG, TST or nutritional status." This appears to be an overstatement which arbitrarily puts the whole family under a cloud with consequent social stigma and even partial failure in compliance by those who really need to take it. Secondly, are we justified to give single drug chemoprophylaxis with INH which has a resistance rate of >5% in our community? What would be the overall impact on INH resistance?
5. INH chemoprophylaxis in all TST positive cases has been recommended for 6 months. What is the evidence to support this conclusion? Duration of

immunosuppressant drugs is variable ranging from weeks to months. So, how can 6 months chemoprophylaxis be universal?

6. The statement "a child born to mother who was diagnosed to have TB in pregnancy should receive prophylaxis for 6 months, provided congenital TB has been ruled out" has not been supported by clinical and investigatory approach for of ruling out congenital tuberculosis. It is of paramount importance to diagnose a case of congenital TB and treat as a new case as early as possible as untreated disease is invariably fatal [5]. Therefore, diagnostic algorithm of congenital TB must be included in the guidelines both for exclusion as well as for treatment.

CM KUMAR AND AK PATWARI
Department of Pediatrics
Hamdard Institute of Medical Sciences and Research,
Jamia Hamdard, New Delhi 110 062, India.
cmkumar1@rediffmail.com

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REPLY

In reference to letter received from Kumar and Patwari, we would like to add that:

1. The current recommendations [1] highlight that the diagnosis of TB is most reliable with microbiological methods and in such cases the findings on chest skiagrams usually do not help any further in diagnosis. Chest skiagram, however, may be done, for detailing the pulmonary disease, depending upon the feasibility.

2. They themselves have pointed out, the existing PCR-based tests available in most commercial laboratories are not reliable therefore these were clubbed with all other inaccurate diagnostic tests. With the advancement in technologies, the guidance may be revised in future as and when new tools or evidence emerges. Cartridge-based nucleic amplification test is one such test currently being evaluated.

3. DOTS for new cases does not need a skilled person as there are only oral drugs to be administered. School based DOTS may be an option but the limited capacities and lack of time or motivation with in the school staff as well as the potential risk of stigmatisation are the likely hurdles Also, partnerships for provision of directly supervised treatment must have a continued link with health providers to monitor the child for response to therapy, adverse events and management of other co-morbidities, including malnutrition. There is certainly a need to make DOTS more user-friendly for children and there is a need to pilot test to achieve innovative out of the box alternatives (school based, home based or neighbourhood DOTS).

4. INH prophylaxis is the only proven and established chemoprophylactic drug for tuberculosis [2-4]. The committee after reviewing the scientific literature and deliberating on programmatic implementation the committee opined that INH therapy should continue to be the mainstay of chemoprophylaxis in our country; albeit at a higher dosage of 10 mg/kg body weight per day.

5. The prophylaxis is recommended for all asymptomatic contacts (children under the age of six years) of smear positive tuberculosis because (*a*) the exposure to an infectious case (which is usually a smear positive TB case) is one of the strongest determinant for the risk of infection, (*b*) and at a younger age the risk of developing disease after infection is very high. Though tuberculin skin test (TST) is performed to establish infection, it may not be required when there is a definite exposure. The current recommendations merely simplifies the mechanism to clinically identify children, in the family/household, who are likely to be recently infected.

   The current evidence is for the post exposure prophylaxis and is recommended for six months. The benefit of a prolonged or continuous use of INH prophylaxis for TB, in a continued state of immunosuppression is not known. We, therefore, found it appropriate to recommend six months prophylaxis only for those cases who are found to be infected at the first point when the immunosuppressive therapy is started.

6. The recommendations clearly state the need to rule out active disease before initiating any child on preventive therapy including suspected perinatal

cases. Congenital TB is suspected based upon clinical examination (hepatosplenomegaly with or without pneumonia), chest skiagrams, microbiological diagnosis and ultrasonology of the abdomen for any hepatic granulomas, particularly in a neonate born to a mother who is suffering from active tuberculosis.

VARINDER SINGH AND BN SHARATH
4vsingh@gmail.com

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Pediatric Tuberculosis

BALJINDER KAUR
Assistant professor, Department of Pediatrics
GMC and RH Patiala, Punjab, India.
banga.baljinder@yahoo.com

I read the recent updated guidelines for pediatric tuberculosis in India with interest, and found them to be informative. However, there may be practical difficulty in evaluating exact weight loss which has been defined as weight loss more than 5% of highest weight recorded in 3 months [1]. Weight loss in terms of percentage can only be defined if previous weight of the child is known. Common presentation of children belonging to rural area is anorexia, fever and complain by parents of weight loss as measured from dress size.

What are suggestions of the authors regarding interval between subsequent repetition of tuberculin sensitivity test as TST is being used as a tool to diagnose pediatric tuberculosis in conjunction with sputum and gastric lavage microscopy along with chest X-ray; every time child presents with unexplained fever, anorexia and weight loss. Should it not be recommended to keep a record of tuberculin sensitivity testing.

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REPLY

In response to Kaur, we wish to state that (*a*) while it is true that the weight records may not be available in many situations but objectively defining these symptoms to cleanly identify disease suspect leads to a better yield as it will improve the performance of the diagnostic algorithm. In the event where the exact weight loss cannot be quantified, one may still investigate for TB if the clinical suspicion is high; (*b*) prior TST testing, even when repeated, is not considered likely to give rise to false positive reactions.

VARINDER SINGH AND BN SHARATH
4vsingh@gmail.com

Tuberculosis - A Quest Towards Objectivity

I read with interest "updated National Guidelines for pediatric tuberculosis in India, 2012" and appreciate the effort made to clarify certain grey areas of interpretation like weight loss or no weight gain besides presenting the contents as flow diagrams for ready reference [1]. I would like to draw attention to certain points requiring further clarification to enable a clinician to use these guidelines practically and effectively in a wider range of situations.

According to figure 1a and 1b, a symptomatic sputum negative patient undergoes chest X-ray and TST. Following this, the possible results would be in six ways as per the outcome of these two investigations.

Chest X-ray can be read as: (*a*) Highly suggestive of tuberculosis, (*b*) Non- specific shadows (*c*) Normal; TST can be read as: *(i*) Positive, *(ii*) Negative. Though most of the possible scenarios are dealt with properly, it does not provide an approach for (a+ii) that is highly suggestive XRC and TST negative. Similarly it does not justify the

use of TST when XRC shows non- specific shadows as no decision is based on TST results whether positive or negative.

CT scan is a useful diagnostic modality in children when tuberculosis is suspected and the radiographic findings are normal or inconclusive [2]. Chest CT can help to identify enlarged, calcified, necrotic mediastinal lymph nodes, which are less frequently found in community acquired bacterial pneumonia and frequently obscured by thymic shadows on chest radiographs of children [3]. It may also detect pulmonary parenchymal lesions not otherwise visualized on chest radiographs [4]. Therefore, a TST positive, sputum negative clinical suspect in such scenario may be subjected to CT scan chest as first investigation (wherever possible) before taking on other investigation for alternate diagnosis.

As tuberculin skin test is defined with the use of tuberculin 2 TU and its procurement is difficult outside government supply, it would be useful to share the manufacturer of such product.

A GUPTA
Department of Pediatrics and Neonatology,
Fortis Hospital and Research Centre, Faridabad, India.
dramitgupta2001@gmail.com

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REPLY

The author has raised the issue about dealing with children with highly suggestive radiology, who are TST negative. With certainty it is spelt out in the diagnostic algorithm that a presumptive pediatric TB case with TST negative and chest *X*-ray findings suggestive of TB should be diagnosed based on *X*-ray findings; because the TST suffers from lack of sensitivity and specificity, and there are operational issues concerned with performing the test efficiently. In view of radiation risk and issues pertaining to CT interpretation (low specificity and inter observer variability) [1,2] it is neither necessary nor appropriate to recommend CT scan as first line investigation. However, the algorithm has identified situations where an expert opinion is needed and they may ask for more detailed investigations including CT chest.

VARINDER SINGH AND BN SHARATH
4vsingh@gmail.com

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