Intramuscular Vaccination in Hemophilia

I read the recent article on hemophilia with interest(1). It is stated that all intramuscular injections are contraindicated and affected children should receive all vaccines including immunizations against hepatitis B and A. Considering the two recommendations together, how should one vaccinate hemophilic children against DPT, hepatitis B and A and *Haemophilus influenzae* type b (which are recommended by intramusclar route only)? This issue assumes further importance as many such vaccines are given during infancy when clinical bleeding episodes are rare since the child is not yet fully mobile.

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REFERENCE

1. Kushyap R, Choudhry VP. Hemophilia. Indian Pediatr 2000; 37: 45-53.

Reply

Children with hemophilia are at higher risk of developing muscular hematoma following intramuscular injections. Therefore, it becomes essential that all Pediatricians should take detailed family history of bleeding episodes. In presence of a positive family history, the children need to be investigated by coagulation studies to identify the cause of bleeding. In the absence of investigative facilities and if the investigations are being deferred for any other cause; it is advised that all suspected cases with bleeding disorders should be vaccinated only by subcutaneous (SC) injections with fine 26 gauze needle. It has been clearly shown that the effectiveness of various immunizations is same irrespective of the method of administration (SC or IM). Site of immunization should be pressed for 10-15 minutes after vaccination. Aspirin should not be used as an antipyretic agent if required.

Children with hemophilia are at higher risk of developing blood transmitted infections such as hepatitis B and cytomegalo virus. Therefore it becomes mandatory that all hemophilic children should receive hepatitis B vaccine subcutaneously at diagnosis in addition to other vaccinations as recommended by IAP.

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Clinical Profile and Sero-Conversion Pattern of Children with HBsAg Positivity

We read with interest the 'Brief Report' on "Clinical profile and sero-conversion pattern of children with HBsAg positivity"(1) and want to make some comments. The diagnosis of acute viral hepatitis-B was made in majority of the study population (40 of 45) on the basis of HBsAg positivity only. However, the diagnosis of acute hepatitis-B infection is made by demonstrating IgM anti-HBc. Of these 40 children, serum bilirubin was normal in 2 and transaminases were not elevated in 3. How can one make a diagnosis of acute viral hepatitis-B, when liver function tests are normal and only

HBsAg is positive? Obviously some of these cases were asymptomatic carriers.

One child was diagnosed to be a case of neonatal hepatitis due to perinatally acquired HBV because she was HBsAg positive. Perinatally acquired HBV means acquisition of HBV infection from mother to child at birth or in the first few months of life. In this case both parents were negative for HBsAg. Moreover, natural history of perinatally acquired HBV infection is altogether different than horizontally acquired HBV. In the life cycle of HBV in the human host, there are 4 stages(2). The first stage is characterized by "immune tolerance". In the healthy adult, this period lasts for 2-4 weeks but in perinatally acquired HBV this period lasts for several decades. In this stage the patient remains asymptomatic and liver function tests (LFT) remain normal in the presence of replicating HBV. (HBsAg +ve, DNA strongly +, HBeAg +). In the second stage, an immunological response develops or improves (also called immune clearance stage). The patient becomes symptomatic with abnormal LFT and harbours replicating HBV. When the host is able to mount a response that eliminates infected cells or greatly dininishes their number, active viral replication ends and the third stage begins. In this stage there is seroconversion of HBeAg to anti-HBe, HBsAg is still positive but DNA is detectable by PCR only (low concentration) and LFT is normal. The stage four or complete resolution of HBV infection stage occurs when HBsAg becomes negative and anti HBs becomes positive and HBeAg and DNA are negative. Therefore, the patient who cleared her HBsAg at 17 months of age is no-way fitting in the perinatally acquired HBV infection category. Most probably she acquired HBV infection through her multiple exposure to various forms of treatment.

"Seroconversion" means conversion of HBeAg status to anti HBe status which is seen in the stage 3 of the disease(2). On the other hand conversion of HBsAg to anti HBs is called complete resolution of infection and seen in stage 4 or immune stage. But in this article the word 'seroconversion' is used inappropriately.

Lastly, carrier rate in this study is very low (only one of 45 case). It has been shown that carrier rate in children is higher than in adults(2). In 0-4 years age group it is 30%, 5-9 years 20% and 10-20 years 10%(2,3). The low carrier rate in this study may be because of false positive HBsAg in many cases. It has been shown that latex slide test has a low sensitivity (45%) but high specificity (upto 100%)(4). That means positive latex slide test may include many false positive cases. This test is used for screening only and once positive should be confirmed by ELISA which was not done in this study. Other facts supporting this point are very low conversion of HBsAg to anti HBs (24%) and 2 of 3 children who died of acute liver failure and Wilson's disease. It has been shown that conversion of HBsAg to anti-HBs occurs in 80% of cases(5) and the window period (core window) varies from few days to several months. The low conversion to anti-HBs in this study may be because of either false positive HBsAg or inadequate follow-up. Follow-up criteria is also not clear in this study. It has been mentioned that they were followed up till anti-HBs was found positive, but only 24% were found positive for anti HBs. For how long the remaining 76% were followed-up is not clear.

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REFERENCES

1. Bai SS, Francis L, Vijayan EK, Suma MS, Urmila KE, Cherian A. Clinical and sero-

conversion pattern of children wih HBsAg positivity. Indian Pediatr 1999; 36: 1243-1248.

2. Lee WM. Hepatitis B virus infection. N Engl J Med 1997; 337: 1733-1744.

3. McMahon BJ, Alward WLM, Hall DB, Heyward WL, Bender TR, Fancis DP, *et al.* Acute hepatitis B virus infection: Relation of age to the clinical expression of disease and subsequent development of the carrier state. J Infect Dis 1985; 151: 599-603.

4. Keating LJ, Silvergleid AJ. Hepatitis: A Technical Workshop. American Association of Blood Banks, Washington DC, 1981.

5. Barker LF, Peterson MR, Shulman NR, Murry R. Antibody response in viral hepatitis, type B. JAMA 1973; 223: 1005-1008.

Reply

The children with viral hepatitis were detected by the presence of fever, anorexia, nausea, vomiting, high colored urine and hepatomegaly. Two of them had normal bilirubin levels and in six of them transaminase values were normal. But they were not the same patients. Anicteric hepatitis is a well known entitiy in viral hepatitis B(1).

Perinatal acquisition of HBV from mother to baby occurs mainly at birth. But 2.5% of babies born to affected mothers get intra-uterine infection(2). Transplacental transfer of HBV occurs mainly during third trimester(3) and less commonly before that(4). But only 70-90% babies develop carrier state due to immunological tolerance. The etiological role of HBV in neonatal hepatitis progressing to cholestasis is well established. The youngest baby in the study group, though presented to us at 8/12 age, had jaundice from 2nd day of life onwards. At the time of admission, her parents were HBs Ag negative which does not mean that they would have been HBsAg negative previously also. All infective and metabolic causes of neonatal hepatitis were ruled out in this baby by appropriate investigations. She had progressive derangement in liver functions and HBsAg was repeatedly positive upto the age of 17 months. The most appropriate diagnosis for this baby is neonatal hepatitis due to HBV.

The term sero conversion indicates conversion of HBeAg to anti HBe status and HBsAg to anti HBs status(5). In the reference quoted by the authors(6), it is not written that sero conversion means specifically conversion of HBeAg to anti HBe status.

In this study group of children with mean age 6 years and 2 months, carrier rate is 15.5%(7) and not one in 45. As stated by the authors, in the age group 5 to 9 years, carrier rate is 20% but not in Indian children. The main factor influencing the evolution of HBV infection is genetic predisposition of the individual(6). The difference of 4.5% carrier rate has to be explained on the basis of genetic difference between the study groups.

The authors write that latex slide test has a low sensitivity (45%) but high specificity (upto 100%). When sensitivity is low and specificity is high, there is less chance of false positive cases. We can expect an increase in false negative cases only(8). If the positive predictive value is low, then naturally we can expect a higher number of false positive cases, but that value is not mentioned by the authors.

The antibodies against HBsAg may become undetectable in patiens who have recovered fully from infection(6). Hence, 24% anti HBs conversion does not mean false positivity in the study group selected. The children with Wilson's Disease were previously diagnosed cases with liver derangement and were on irregular treatment. Superadded HBV infection would have precipitated acute liver failure. The follow up criteria and period of follow up are