Selected Summaries

Disseminated BCG Infection

[Casanova JL, Blanche S, Entile JF, et al Idiopathic Disseminated Bacillus Calmette-Guerin Infection: A French National Retrospective Study. Pediatrics 1996; 98: 774-778.]

Disseminated Bacillus Calmette-Guerin (BCG) infection after innoculation of live vaccine is considered to result from impaired immunity. However, in half of the cases, regarded as idiopathic, no well-defined immunodeficiency condition can account for the infection. The objective of this study was to report the prevalence, clinical features, associated infections, and outcome of children with idiopathic disseminated BCG infection.

This was a national retrospective survey during the period from 1974 through 1994 in which all Neonatology and Pediatric Units in primary care and referral centers throughout France were included. Selection criteria included BCG infection, dissemination to at least two areas beyond the inoculation site, and no well-defined immunodeficiency condition. Sixteen children (8 girls and 8 boys), born to families unrelated to each other but often consanguineous (5 of 16), satisfied the criteria; 11 children were born in France and 5 abroad.

The minimal prevalence rate was estimated at 0.59 cases per 1 million vaccinated children born in France. Clinical features included fever and cachexia, disseminated BCG infection to lymphnodes (15 of 16), skin (13 of 16), soft tissues (11 of 16), lungs (11 of 16), spleen (11 of 16), liver (11 of 16), and bones (9 of 16). Eight Children had associated or subsequent severe opportunistic infection (50%), with either nontyphi Salmonella enterica serotypes (7 of 16) or Mycobacterium abscesses (1 of 16).

All the 16 children were reported as being healthy before vaccination. They were vaccinated with live BCG either by scarification or, more recently, by multipuncture. All children but 3 were vaccinated with BCG substrain Pasteur, and although the lots differed, the dose administered was always 25 mg. The age at vaccination varied form 1 week to 11 months. For 15 children, the onset of symptoms occurred between 1 and 5.5 months and for a 16th subject, 14.5 months after BCG vaccination. Clinical generalization of the infectious process and bacteriologic diagnosis occurred after a delay ranging from 1.5 to 26.5 and 2.5 to 36.5 months, respectively. Inflammatory markers, namely blood erythrocyte sedimentation rate, serum C-reactive protein, and fibrinogen, were elevated in all children. BCG was cultured from all children. Tuberculin-induced, delayed-type hypersensitivity *in vivo* was found to be positive (>10 mm induration) in 14 (87.5%) of 16 children. In addition, serologic tests for BCG were positive in all children tested in this series (9 of 16). The outcome was poor; 8 children (50%) died; the cause of death was BCG infection for most children (7 of 8).

A central question regarding children with idiopathic disseminated BCG infection is whether the infection results from a childhood immunodeficiency or from an increased virulence of the BCG. Even the least virulent substrains, such as BCG Russia and Japan, may cause disseminated infection, arguing against the latter hypothesis. In addition, BCG from the same batch,

when injected into other children, was always found to be innocuous, further ruling out a BCG mutation selected *in vitro.* Moreover, BCG directly cultivated from infected children, when injected into guinea pigs, was not found to be pathogenic, arguing against a BCG mutation selected *in vivo.* Although unlikely, a BCG mutation selected *in vivo* that would enhance virulence toward humans only cannot be ruled out.

Instead, the hypothesis of an unclassified inherited childhood immunodeficiency is strongly supported. In the literature five familial forms of disseminated but idiopathic BCG infection were reported; four pairs of siblings and one pair of first cousins (10 [17%] of 60 children). Moreover, among the single-case families, parental consanguinity has been found in one third of the families. Taking into account the equal number of boys (n=36) and girls (n=23) (1 unknown), the available data suggest autosomal recessive inheritance. Further evidence in favor of a human immunodeficiency condition arises from the observation in this series that 7 children (43%) also had other severe infections.

Thus, this study shows that idiopathic disseminated BCG infection is a rare but severe complication of BCG vaccination. The infection probably results from an as yet unknown genetically determined immunodeficiency condition that affects the killing of intracellular bacteria such as BCG and Salmonella.

Comments

Based on a review of the world literature and a French national restrospective study, it found that four well-defined immunological conditions - severe combined immunodeficiency (SCID), complete Di George syndrome, chronic granulomatous disease, and acquired immunodeficiency syndrome (AIDS) - were implicated in 61 of 121 cases of disseminated BCG infection(l). However, no defined immunodeficiency could account for the remaining 60 infections, which were thus regarded as idiopathic.

Of the above mentioned four immunodeficiency disorders, AIDS is the most common. Since BCG vaccination in early infancy is a routine in our country and AIDS is unlikely to be diagnosed in early infancy in the present scenerio even if the child is suffering from it, inadvertent BCG vaccination in such children is not totally avoidable. In another report from France 2 of the 68 HIV infected children vaccinated with BCG before the diagnosis of HIV infection was suspected, developed vaccine related complications^), Seven of these children had a large satellite adenopathy with or without skin fistulae, whereas the other 2 had disseminated BCG infection. Similarly, while reporting a case of disseminated BCG infection in a HIV infected child, 7 more similar cases were reviewed from the literature(3).

Currently the World Health Organization and United Nations Children's Fund policies support the routine immunization of asymptomatic infants in countries with high rates of both HIV and tuberculosis infection. Also, the rising incidence of tuberculosis in advanced countries like USA and a close link between HIV infection and TB have revived the debate of vaccinating HIV infected children with BCG. However, for children living in the United States, a joint communication from two centers for Disease Control and Prevention Advisory Groups, the Advisory Council for the Elimination of Tuberculosis and the Advisory Council for Immunization Practices, has recommended that BCG vaccination should not be given to HIV-seropositive or

known infected infants and children, even if the risk of tuberculosis is high(3). In France vaccination with BCG, which is compulsory before 6 years of age and is often carried out on the first few months of life, is contraindicated in HIV-infected children^).

Overall, the arguments for and against are interesting and the controversy remains.

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REFERENCES

1. Casanoava JL, Jouanguy E, Lamhamedi S, Blanche S, Fischer A. Immunological conditions of children with disseminated BCG infection. Lancet 1995, 346: 581.
2. Besnard M, Sauvion S, Offredo C, *et al.* Bacillus Calmette-Guerin infection after vaccination of human immunodeficiency virus-infected'children. Pediatr Infect Dis J 1993,12: 993-997.
3. Edwards KM, Kernodle DS. Possible hazards of routine Bacillus Calmette-Guerin immunization in human immunodeficiency virus-infected children. Pediatr Infect Dis 11996,15: 836-838.

Sucrose: Is It Not Only Sweet, But Also An Analgesic?

[Allen KD, White DD, Walburn JN. Sucrose as an analgesic agent for infants during immunization injections. Arch Pediatr Adolesc Med 1996; 150: 270-274.]

The potential application of oral sucrose as a benign analgesic agent for use in pain management for infants has evoked considerable interest. A double blind randomized controlled trial was conducted in Nebraska to assess the effectiveness of sucrose as an analgesic agent during routine immunization injections. Two hundred and eighty five consecutive subjects were selected from infants of normal gestation (minimum 37 weeks) who presented for regular immunization. These infants were randomly assigned to one of the three treatment groups: a no intervention group, a control group (sterile water group) or an experimental group (12% sucrose solution group). Two minutes prior to the appropriate injections the infants were administered orally 2 ml of sterile water or 12% sucrose as per their groups. Audio and video-tape recordings of all subjects were made throughout the administration and for three minutes after the injections. The proportion of crying (defined as "audible distress vocalizations") per 15 second interval was then recorded by a trained primary observer, reliability of which was found to be 97% by a second observer. ANOVA models were made to statistically evaluate the difference in the proportion of time that was spent crying across treatment groups, age groups, number of injections, and length of time required for injections.

Contrary to previous research, the results of this investigation found that oral sucrose administered prior to injections did not produce significantly less crying in infants than did a sterile water solution. Both sucrose and sterile water solutions resulted in significantly reduced behavioral pain responses in 1 to 2 weeks old infants compared with those of same age who received no intervention ($p < 0.005$). Older infants,

those who received water or sucrose, cried significantly less only if they were administered one injection rather than two injections ($p < 0.05$). Results also indicated that none of the variables including condition and time required to administer injections or the nurse who administered injections contributed significantly to the prediction of crying for injections.

Comments

The ability of a neonate to perceive and react to pain has been much debated in the recent past. Most of the anatomical pathways and neurotransmitter functions necessary for pain perception are fully developed in newborns. Although infants cannot verbally describe pain, the experience may have profound psychological and physiological effects. These physiological changes by themselves may not be detrimental to the well being of a healthy term neonate but they do indicate a stress directional change.

Even in 1930's and 1940's it was a practice in some hospitals to use "sugar nipples" or "sugarball anesthesia" (sugar dropped into a gauze sponge tied to form a sac approximately the size of a rubber nipple dunked in whisky) for newborns undergoing circumcision. Newborns were allowed to suck on such nipples dunked in whisky even for abdominal surgeries where total muscle relaxation is not paramount.

In an early experimental study(l) on 10 day old rats, administration of intraoral infusions of 3.5%, 7.5%, and 11.55% sucrose all increased latency before each animal lifted its paw off a hot plate. It was subsequently shown(2) that 2 ml of 12% intraoral sucrose reduced the duration of cry by more than 50% in newborn babies subjected to heel prick or circumcision. A later cross over trial(3) showed that when newborn infants were administered sucrose, the calming effect was rapid, substantial and lasted for at least four minutes. For the 6 weeks old infants this effect lasted for only 1 minutes. In a larger randomized double blind placebo controlled trial(4), neonates were administered either sterile water or 12.5% or 25% or 50% sucrose solution two minutes before heel prick; it was concluded that concentrated sucrose solution seemed to reduce crying and the autonomic effects of a painful procedure. Another study(5) demonstrated that the most effective time delay between oral administration of sucrose and the painful stimuli is 120 seconds. It also concluded that the analgesic effect of sucrose is not influenced by either concentration or volume.

The present study evaluated the efficacy of sucrose as an analgesic agent when administered without sucking response, across a large sample of infants (2 weeks to 18 months old). The authors also studied the impact of sucrose as a function of the number and speed of immunization injections. The findings are similar to an earlier report(6) in which also, no significant difference could be documented in the duration of crying between two groups of infants who were given either 2 ml of 7.5% sucrose of 2 ml of sterile water before heel prick.

Results of the current study suggest that the calming effect could be attributed to a feature common to water and sucrose *(e.g.,* a consummatory response or ingestion of palatable substances) rather than a feature specific to sucrose. It is still unknown whether large concentrations of sucrose might have proportionately stronger analgesic effects. Further research is also needed to explore the additive effects of sucrose and the sucking response. In this study, the data collected was restricted to measures of crying and might have missed changes in

other behavioral pain responses such as heart rate and body movements.

One would like to see more concrete and consistent data before prescribing sucrose or water as a routine prior to injectable immunization.

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REFERENCES

1. Blass E, Fitzgerald E, Kehoe P. Interac tions between sucrose, pain and isolation distress. Pharmacol Biochem Behav 1987; 26: 483-489.
2. Blass EM, Hoffmeyer LB. Sucrose as an analgesic for newborn infants. Pediatrics 1991; 87: 215-218.
3. Barr RG, Quek VS, Cousineau D, Oberlander TF, Brian JA, Young SN. Effects of Intra oral sucrose on crying mouthing and hand mouth contact in newborns and 6 week old infants. Dev Med Child Neurol 1994; 36: 608-618.
4. Haouari N, Wood C, Griffiths G, Levene M. The analgesic effect of sucrose in full term infants: A randomized controlled trial. BMJ 1995; 310:1498-1500.
5. Blass EM, Shah A. Pain reducing properties of sucrose in human newborns. Chem Senses 1995; 20: 29-35.
6. Rushforth JA, Levene MI. Effect of sucrose on crying in response to heel stab. Arch Dis Child 1993; 69: 388-390.