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RESULTS OF SURVEILLANCE FOR BCG COMPLICATIONS IN SAKHA REPUBLIC (YAKUTIA)

Summary

Results of monitoring for complications to BCG vaccine in children in Sakha Republic (Yakutia) are presented. Incidence and nature of complications to vaccines against tuberculosis infection and the clinical structure of complications were analyzed; causes of complications were determined. For the last years, we observed growing incidence of complications to vaccines against tuberculosis. The study established that complications develop most often to BCG vaccine, and rarer to BCG-M vaccine. Lymphadenitis was the prevailing diagnosis in the clinical structure of complications. Severe forms of complications were registered more frequently in children under 3 years of age. Complications in children immunized at pediatric polyclinics or rural first aid posts were mostly due to wrong administration technique. Main causes for complication development were: perinatal pathology, underestimation of counterindications, infectious or virus diseases in postvaccinal period, faults in vaccine administration technique.

Keywords: BCG vaccine, tuberculosis, pediatric population

Introduction. BCG vaccine was created in 1921 by French microbiologist Albert Calmette and veterinarian Camille Guerin for human immunization against tuberculosis. In USSR, BCG vaccine was introduced in 1925. Later, results from experimental and clinical studies were systematized, showing the effectiveness of vaccination: mortality from tuberculosis in vaccinated groups of children exposed to bacillary-positive persons was significantly lower than among non-vaccinated children. In our country, starting in 1928, BCG vaccination had been recommended for newborns from the infectious disease foci, and starting in the 1950s vaccination was made mandatory all over the country [1].

Today according to national immunization schedule, vaccination to prevent tuberculosis in children is done on days 3-7 after birth; revaccination is done in 7 and 14 year old children. In Sakha Republic 93-95% of newborns in maternity hospitals are covered with BCG vaccination annually; coverage at age 1 is 98-98.4%. The first revaccination covers 82-85% of predicted

population; the second revaccination covers 60-78% of children.

In 2010, 994 children in Sakha Republic did not receive BCG, which is 6.9% of newborns (880 in 2009; 718 in 2008). Among vaccination counterindications in newborns, the first reason was premature birth (19.2%), and the second and third reasons were perinatal encephalopathy (14.4%) and intrauterine infection (9.3%), respectfully.

The problem of complications after BCG vaccination and revaccination has grown important for the last years. In view of this, in 2003 a new patient follow-up group was established and added to existing groups of patients followed-up in anti-tuberculosis dispensaries: group V for children with complications after vaccines against tuberculosis (Order #109, issued March 21, 2003). This enabled precise monitoring of the incidence of complications to vaccines against tuberculosis and improved registration and follow-up of this patient population.

According to the Order #109 (issued March 21, 2003) complications developing after BCG vaccination are divided to 4 classes:

Class 1 complications: localized lesion (subcutaneous infiltrate, cold abscess, ulcer), regional lymphadenitis;

Class 2 complications: persisting or disseminated BCG infection without lethal outcome (lupus, osteitis);

Class 3 complications: disseminated BCG infection, generalized pathology with lethal outcome, observed in cases with congenital immune deficiency.

Class 4 complications: post BCG syndrome (erythema nodosum, granuloma annulare, skin rash).

By official statistical reports, postvaccinal complications are found in nearly 300 newborns annually in Russian Federation. M.V. Shilova notes that in Russian Federation in 2010 the most severe complications (dispensary follow-up group VA) were registered in 154 children (132 in 2009; 105 in 2008), which made 0.7/100.000 pediatric population (0.6 in 2009; 0.5 in 2008). Complications of medium severity (dispensary follow-up group VB) were diagnosed in 353 children (552 in 2009; 447 in 2008), which was 1.6/100.000 children. The most minor complications (dispensary follow-up group VV) were found in 82 children (76 in 2009; 105 in 2008) or 0.4/100.000 pediatric population. Hence it is seen that complications after tuberculosis vaccines have been aggravating in terms of clinical structure and incidence [2].

In 2008 the regions of the Russian Federations with the incidence of tuberculosis lower than 70.0/100.000 population switched to vaccination of newborns with BCG-M vaccine, in compliance with the Order of the Russian Federation Ministry of Health and Social Development #673 (issued

October 30, 2007) “On national immunization schedule based on epidemic indicators”. Because of persisting high incidence of tuberculosis on the territory of Sakha Republic, newborns had been vaccinated with BCG vaccine until 2009. Use of BCG-M vaccine has started only in July 1, 2009, following the Order of the Ministry of Health of Sakha Republic (Yakutia) #01-8/4-387 (issued April 15, 2009).

Aim: to assess the results of the monitoring for incidence of complications after BCG vaccines in children in Sakha Republic, and to identify the characteristics and major causes of complications.

Material and methods. We analyzed medical documentation on children who developed complications after BCG vaccination for the period from 2003 to 2011. Total of 63 children with various complications had been followed-up in Republican anti-tuberculosis dispensary, of them 12 (19%) in Group VA, 35 (55.5%) in Group VB, 16 (25.4%) in Group VV. Incidence of complications started to sharply increase in 2005; the largest number of cases with complications to BCG vaccines over the republic was registered in 2009 (19 cases).

Children under 1 year of age made 26.9% of the total number of follow-up patients, with boys predominating (58.7%). In 58 (92.1%) of 63 cases children were vaccinated with BCG, while only 5 (7.9%) were vaccinated with BCG-M. Majority of cases developed complications after vaccination (89%), and more rarely after revaccinations (11%).

By clinical structure of complications, lymphadenitis developed most often and was observed in 39 children (61.9%). Tuberculosis of bones was diagnosed in 10 (15.8%), cold abscess in 6 (9.5%), cutaneous tuberculosis in 3 (4.8%), keloid in 2 (3.2%), ulcer in 1 (1.6%), generalized BCG infection in 2 (3.2%) children with primary immune deficiency.

The most severe complications (dispensary follow-up group VA) with bone and joint involvement and generalized BCG infection were registered only in children under 3 years, including 4 children under 1 year of age.

In all detected cases of complications to BCG vaccine children were prescribed specific therapy either inpatienly in tuberculosis hospital, or outpatiently. The length and treatment regimen depended on nature of complications. Dispensary follow-up was managed with regard to clinical form and class of complication.

Results and discussion. Complications to tuberculosis vaccines were registered most often in children in Yakutsk (42.8%), Mirninsky region (12.7%), Neryungrinsky region (11.1%), and rarer in other regions of the republic.

Analysis of the incidence by health institutions showed that 76.2% of children were

vaccinated in maternity departments, 20.6% in polyclinics, and 3.2% in (rural first aid posts).

There were 15 (23.8%) cases with unfound causes of complications and 48 (76.2%) cases with established causes. Among the established causes of complications, the most frequently identified causes were wrong administration technique (39.7%), program errors (20.6%), and wrong patient appointment for vaccination (15.9%).

Analysis of internal investigation reports showed that the structure of clinical forms of postvaccinal complications directly depended on where the children were vaccinated. Thus BCG-lymphadenitis developed mostly in children vaccinated in maternity hospitals (76.2%), cold abscess – in children vaccinated in polyclinics (75%), keloids and ulcers – in children vaccinated in polyclinics (100%), BCG-osteitis – in children immunized in maternity departments (75%).

Complications to BCG vaccines in children who were immunized in maternity hospitals were distinctly more severe and had more vivid clinical manifestations. 3 of 10 cases of BCG-osteitis developed as result of gross violation of the instructions for use of BCG vaccine, as evident from the fact that blood samples for phenylketonuria test were collected on the day of vaccine administration. High incidence of BCG-lymphadenitis in children who were vaccinated in maternity hospitals or rural first aid posts signalized, as a rule, about wrong appointment of children for vaccination. The nature of complications in children vaccinated in polyclinics showed that they were largely due to technical faults during administration of vaccines.

It should be emphasized that in 16 (25.4%) cases out of 63 complications to BCG were detected with delays. This group (dispensary follow-up group VV) included patients with lymphadenitis in reverse development phase (calcification). BCG-lymphadenitis in reverse development phase was detected by radiological chest examination. This type of complications was difficult to diagnose at early phases because of the scarcity of symptoms during the progression of lymphadenitis, and because no pain syndrome or skin changes were seen at early phases of the disease.

Localized complications (ulcer, cold abscess, keloid) were detected on visit to a doctor. Children were referred to anti-tuberculosis dispensaries from medical districts covered by pediatricians. Patients with cutaneous tuberculosis (3 cases) visited dermatologist first. Average time to referral from primary network to phthisiologist was 1.5 to 2 months.

Cases of BCG-osteitis were the most difficult to correctly diagnose. After thorough history taking visible counterindications to BCG vaccination were absent in 88.8% of children with BCG-osteitis; the fact of trauma in postvaccinal period was ascertained in 37.5% of patients; superimposition of acute virus or other infections was established in 25%; vaccination against DPT

was present in 37.5%. These children were not exposed to persons with tuberculosis disease. Precipitating factors (trauma, intercurrent diseases etc.) were present. Various localizations of bone lesions were observed in patients, with a picture of reactive arthritis in earlier stages of the disease, followed later by osteomyelitis. Moreover, circumscribed involvement of bone tissue was observed, with the absence of lung or intrathoracic lymph node involvement. There was notable disparity between rather extensive bone destruction and the "mild" disease progression with scarce clinical manifestations and with periods of remission and exacerbation in BCG-osteitis, unlike in non-specific diseases of osseous-articular system. Clinical picture was characterized most often by heightened temperature, gait abnormality, swelling, and absence of marked intoxication syndrome.

It should be pointed out that in Sakha Republic awareness among primary network specialists (pediatricians and pediatric surgeons) has considerably raised for the last years, in what regards the management of patients with this disease. As a result, patients with osseous-articular diseases referred for operation to surgical department of Pediatric Center of the Republican Hospital No.1 (National Center for Medicine) undergo histological and bacteriological examinations, and have consultation with the phthisiologist.

Etiologic confirmation is important in verifying osseous-articular tuberculosis and BCG-osteitis. Reasons for the necessity of etiologic confirmation in children are: differences in organization of antiepidemic activities, chemotherapy regimens and substantive actions, which are taken into account during the diagnosis of either tuberculosis disease, or complication to BCG vaccination.

In 9 of 10 cases of BCG-osteitis vaccine strains of tubercle bacilli (M.bovis-BCG) were present in surgical material. Histological confirmation of the diagnosis was established in 10 patients with BCG-osteitis. Importantly, 2 species of staphylococci (S.aureus and S.epidermidis) were cultured in operative material from 3 (30%) patients. Sensitivity to tuberculin in children was moderate, judging by the results of Mantoux test with 2 TU; mean papule size was 11.3$\pm$1.3 mm. Diaskintest used in our republic since 2009, was negative in 3 patients; this test was not used in other patients.

All patients with BCG-osteitis received consultation in the Federal State Budgetary Institution "Saint-Petersburg Research Institute for Phthisiopulmonology". All 10 patients underwent surgical treatment, of them 8 patients were treated by high-tech surgery.

Conclusion. Results of monitoring for complications to tuberculosis vaccines in Sakha Republic showed growing number of complications to BCG vaccine. Complications were registered most often in children under 1 year, vaccinated with BCG, or much rarer with BCG-M vaccine. The

most severe complications with marked clinical manifestations developed in children who were vaccinated in maternity hospitals, signalizing failure to determine indications and counterindications to vaccination. In children who were vaccinated in pediatric polyclinics or rural first aid posts complications develop more often due to faults in administration technique. Perinatal pathology, underestimation of counterindications, infectious and viral diseases in postvaccinal period contribute to development of complications to BCG vaccine. All of the above said requires strengthening of measures to control the quality of BCG vaccination and revaccination.

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