Benghazi University

Faculty of medicine

THE OUTCOME OF POST BACILLUS CALMETTE GUERIN VACCINE LYMPHADENITIS IN BENGHAZI CHILDREN HOSPITAL

2005-2010

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LIST OF ABBREVIATIONS

AFB	Acid Fast Bacilli
AIDS	Acquired immune deficiency syndrome
ATT	Anti-Tuberculous Treatment
BCG	Bacillus Calmette Guerin Vaccine
CBC	Complete blood count
EPI	Expanded program of immunization
ESR	Erythrocyte sedimentation rate
FNA	Fine needle aspiration
INH	Isonazid
IF-G	Interferon-gamma
PCR	Polymerase Chain Reaction
TB	Tuberculosis
TH	T-helper cells
TST	Tuberculin skin test
WHO	World Health Organization

بسم الله الرحمن الرحيم

وما بكم من نعمة فمن الله.....

سورة النحل

صدق الله العظيم

Certificate

I certify that the research study entitled **(The outcome of post BCG Lymphadenitis in Benghazi children hospital 2005-2012)**was prepared under my supervision in partial fulfilment of the requirement for the degree of master in paediatrics**.**

……

Dr. Kheiria M. Bugalawi

In view of the available recommendation, I forward this thesis for debate by the examining committee

……..

Dean

We are the examining committee; certify that we have read this thesis and have examined the student in its content and that it is adequate as a thesis for the degree of master in paediatrics

…… ……

President member

……

Dr.

Dean

Benghazi University

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Dr. HUDA M. ELSHARKASI

DEDICATION

I WOULDL LIKE TO DEDICATE THIS STUDY TO MY PARENT, MY

HUSBAND,MY SON AND ALL THOSE SUPPORTED ME.

Dr. H.ELSHARKASI

LIST OF CONTENT

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ABSTRACT

BACKGROUND AND OBJECTIVE :

Bacillus Calmette Guerin (BCG) vaccination for protection of tuberculosis has been in use for long .Although the vaccine is safe in immunocompetant child ,but it's administration can result in complications , BCG lymphadenitis is the most common complication of BCG vaccine and accounts for about 98% of BCG complications .To our knowledge there is paucity of published data in this topic ,so we consider it is important to spot the light on clinical presentation of diseases ,treatment modalities available and outcome of adenitis after BCG vaccination in our community.

***DESIGN AND SETTING*:** Retrospective review of files of the infants presented with BCG lymphadenitis and referred to infectious clinic in Benghazi children hospital.

***METHODS*:** We reviewed all the files of patients presented with BCG lymphadenitis in infectious clinic in the hospital from 2005 – 2010, during this period the infants received two types of vaccine , in 2005 BCG SSI Danish 1331 strain and Indian SII strain in other years. Files reviewed according to age of vaccination , age at presentation, interval between vaccination and development of adenitis , types of adenitis , site and size of lymph node involvement , family history of TB and also CBC , ESR, chest radiography .

RESULTS :

Total number of patients presented with BCG lymphadenitis are 89, male gender was more predominant(60%) , with male to female ratio1.47:1**.** Mean age of presentation was 4.1 months (SD +/ - 3.1) , 60.7% of patients presented between 1-6 months post vaccination and one case developed adenitis 17 months post vaccination. All cases presented with left site involvement of lymph node ,left axilla was the most common site of pathology in 93.3% of cases in isolated or associated with other lymph node , followed by left supraclavicular (5.6%) and less being involved is cervical lymph node (1.1%) **.**90 % of patients presented as single lymph node involvement, 10% presented with multiple lymph nodes**.** Suppurative adenitis

occurred in 54 % of patients, 46 % presented as non suppurative (simple) adenitis . Both types of adenitis resolved spontaneously with mean time of improvement was 6.7 months in all our patients managed conservatively (92 %) of cases: the mean time of improvement in suppurative group was 6.9 months (SD -/+4.1) and for non-suppurative group was 6.5 months (SD -/+3.5) .Six patients underwent to surgical intervention &1 case received ATT before refer to our clinic.

Largest number of cases seen on 2005 (28 patients) and 43 patients (48.3%) during 6 years of study period received the vaccine in Gumhouria hospital .

***CONCLUSION* :**

BCG lymphadenitis associated with high incidence of suppuration, and it follows a benign course in immunocompetent host with complete spontaneous recovery **.** Follow up and family assurance are main stay of the management .

RECOMMENDATION :

- Physician should be aware of normal reaction to BCG vaccine to avoid unnecessary investigation and unneeded admitions to hospital.
- Follow up of patients with BCG adenitis till resolution is required.
- Good nurse training for strict intra dermal vaccine administration is required.
- Files should contain clear and complete information.
- Assurance to family.

***Furthermore we recommend that* :** immunization program manger should be aware of complication of changing BCG strains and suppler should get the vaccine from well trusted manufactures and more researches have to be conducted to evaluate efficacy of used vaccine.

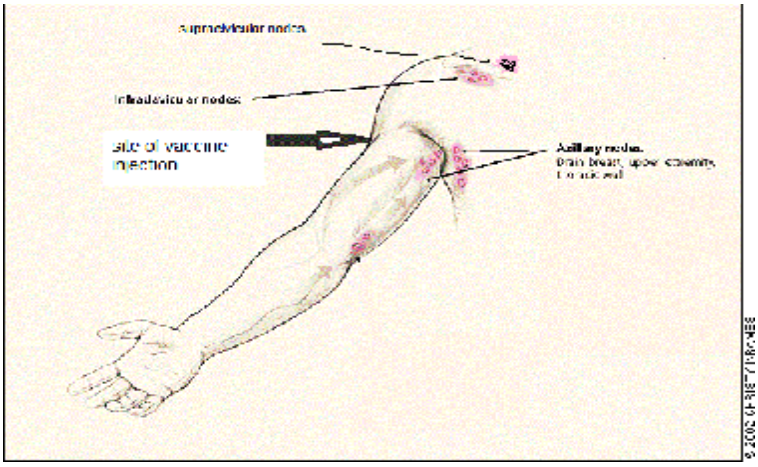
Chapter1

Introduction

INTRODUCTION

BCG lymphadenitis is the most common complication of BCG vaccination[1][2] [3][4] [5] accounts for about 98% of BCG complication, the remaining 2% consist of injection site abscess , ulceration ,arthritis and osteomyelitis [6] .It's seen even in the child with a normal immune response [7][8] ,and doesn't affect the level of protection afforded by the vaccine [7] . The exact incidence of such complication is difficult to estimate as their definitions are not universally accepted and the frequency vary with different countries depending on many host and vaccine related factors, but generally it ranges form 0.1- 1% in different series [7] , mean interval for appearing of adenitis is about 2.5 months following vaccination [7], however it is reported that post vaccine complication developed at age of 18 months and as late as 3 years. [8] [9]

BCG lymphadenitis mainly is seen in ipsilateral site of vaccination [3][4] , > 95%of cases in ipsilateral axillary nodes (Area of drainage) ,the supraclavicular or cervical may occasionally be enlarge [2][3][4] **(**the higher BCG injection site above the insertion of the tendon at deltoid , the higher likelihood of cervical lymphadenopathy **)** [3] in isolation or in association with enlarged axillary nodes , there are only one or two enlarged nodes but multiple glands may be palpable in some cases. [4][3]**)**



After intradermal injection of the BCG ,it starts multiplying rapidly at the site of inoculation and rapidly transported through the lymphatics to the regional lymph gland followed by hematogenous spread of BCG resulting in creation of very small

Foci in different organs , this is called **(**normal BCG-itis **)** [5] , so invasion of regional node by a virulent bacilli and subsequent slightly enlarged regional nodes are part of processes of successful vaccination [8][10][11]and they are rarely noticeable unless searched for it specifically , this subclinical adenitis regresses spontaneously and of no practical importance[3][5][8] .Since there is no specific guidelines or recommendation clearly define and differentiate normal from abnormal and specific agreed definition as what constitutes BCG lymphadenitis particularly with regards to the size of the lymph node enlargement and its onset post vaccination , so generally BCG adenitis is coined with the cases in which enlargement of lymph node becomes enough to easily palpable and to arouse a significant concern for the child's parent to seek medical advice [3] or in cases where suppuration took place, or in cases in which the glands that don't belong strictly to "regional " glands enlarged might be included[5].

The diagnosis of BCG adenitis is mainly clinical [12] depending on:

1. History of vaccination on the same side.
2. Axillary, supraclavicular, cervical lymph node enlargement ipsilateral to vaccination site . [3] [4] [5]
3. Absence of tenderness and raised temperature over the swelling [4].
4. Absence of fever and other constitutional symptoms [3] [4] [8].

Chest radiography, tuberculin test reaction and hematological investigations are not much helpful [4] however fine needle aspiration cytology may be helpful in doubtful cases.

Two forms of BCG lymphadenitis can be seen during the clinical course:

1. Non suppurative form (Simple BCG lymphadenitis).
2. Suppurative form.

Simple BCG lymphadenitis occurs in the beginning and frequently resolves spontaneously without any sequelae within few weeks to months [3] , in some cases affected lymph nodes may enlarge progressively and become suppurative indicated by appearance of fluctuation in the swelling with erythema and edema of the overlying skin with pustule formation [13][14] , suppurative adenitis also can develop abruptly within 2-6 month after BCG [4][13] , subsequent course usually distinguished by occurrence of spontaneous, persistent caseous discharge and sinus formation and

healing takes place through cicatrization and closure of sinus .The whole process takes several months during which wound care may be required [3].

BCG vaccine is a part of national immunization program in Libya and BCG lymphadenitis is the most common complication of BCG vaccination .To our knowledge there is paucity of published data in this topic, so we believe it is important to spot the light on clinical presentation of the disease, treatment modalities available and outcome of adenitis after BCG vaccination in our community.

Chapter 2

Review of literature

REVIEW OF LITRATURE

History of BCG vaccine:

BCG: is alive attenuated Bacillus Calmette, derived by in vitro attenuation of an isolate mycobacterium bovies especially cultured every 3 weeks for 13 years in artificial media at institute of Pasteur in France 1908, named after its discovery by French bacteriologist Albert Calmette and veterinarian Camille Guerin.[15]

The first human trial occurred in July 1921 when it was first administrated orally to newborn infant ,since then cultures of BCG were distributed to many laboratories around the world[7][15] .Nowadays, different vaccines in clinical use have emerged after subculture of parental strain in may laboratories , which have varying phenotypic and genotypic characteristics, so a dozen of distinct daughters strains emerged [16][17][18 including four that are currently in major use , which represent 90% of BCG vaccination worldwide (Pasteur strain 1173 P21 , Tokyo strain 172, Danish strain 1331, Glasxo strain 1077). [19]

BCG immunology:

BCG inoculation induces exclusive cellular immunity in order to provide protection [3][11][20][21][22] the immunity produced can be tested by TST, this takes between 2-10 weeks .Since BCG mycobacterium is an intracellular bacterial pathogen , once inoculated into the body , it resides and multiply within host mononuclear phagocyte , when it presented to T-helper lymphocyte cells **(**TH- 0**)** they differentiate into TH- 1 and memory cells , this takes around 6 weeks , during which vaccinated person becomes TST positive , upon re-exposure to the same antigen , specific memory cells **(**th1**)** are activated and produce cytokines , in particular interferon gamma **(**If-G**)** that activates and attracts macrophage into the area ,it takes 2 -3 days , that's why it's called delay type hypersensitivity or cell mediated hypersensitivity. [11][20][23]

So we can say that BCG vaccine acts by replacing the potentially dangerous primary infection due to mycobacterium TB with innocuous primary infection due to

BCG, thus activating host cell mediated immunity, so an infection with mycobacterium tuberculosis will be of re-infection type [15] and presence of scar at vaccination site indicates that vaccine has been given. [24]

Efficacy of BCG vaccine:

Efficacy of the vaccine in the human has been evaluated in several well controlled studies performed during the twentieth century, that varies from **(**0-80%**)** this variability in its efficacy constitutes the most controversial aspect in its use , the results observed to be dependent on geography[25] .Rosenthal…et al 1961 through a twenty year statistically analyzed study in Chicago reported 74% reduction of morbidity in BCG vaccinated children[26] ,trails in Puerto Rico 1958 demonstrated that BCG vaccine was approximately 30% effective in these population [27] ,another study conducted by the British Medical Researcher Council 1971 among adolescent consistently shown protective effect of more than 80% [28] ,inconsistently trials conducted in South India published 1979 **(**Chingle Put Trial**)** showed no protective effect of BCG vaccination[29],the discrepancies in the results and the reasons for such variable efficacy may be due to:

1. Difference of BCG strains in genetic characteristic and in the quality: genetic variation in the BCG strains used may explains this variability reported in different trials. [16] [25]

2 .Host genetic factor: difference in the genetic make-up of population may explain this variability, but there is arguing against the genetic variation showed a 64% protective effect of vaccine in children born to families whose originated from India **(**where vaccine efficacy has previously been shown to be zero) [29] the result was very similar to the figure derived from UK trails.[30]

3.Interference by non tuberculous mycobacteria: some studies demonstrate that prior immunization with environmental mycobacteria inhibits BCG multiplication and therefore , prevents induction of efficient BCG induced immune response [31].

4. Interference by concurrent parasitic infection: in another hypothesis simultaneous parasitic infection changes the immune response to BCG making it less effective as T-helper 1 cells is required for an effective immune response to

tuberculous infection, concurrent infection with various parasites produce simultaneous T- helper 2 response which blunts the effect of BCG vaccine.[32]

5. Exposure to ultraviolet light: concentration of ultraviolet light from sun may have some effect on efficacy of the BCG vaccine, it is demonstrated that it reduces efficacy of the vaccine in the laboratory / guinea pigs. [33]

6.Patient nutritional status: which in some way effect the response to immunization in general ,the exact relation of malnutrition to immune response is not clear probably, important studies of weight for age status and immune response of kwashiorkor and marasmus and immunity confirm such relationship. [7]

7.Route of administration and dosing schedule of the vaccine: [7] the relation between dose , method of administration to the efficacy of BCG vaccine have been investigated in a lot of studies worldwide , depending on the fact that a given dose, variable application techniques and diverting devise used for vaccination will alter the number of bacilli given, subsequently will change the immune response to vaccination [21][34][35] .Some studies found that Intradermal administration of vaccine produces immune response better than percutaneous route ;a 2004 review article done by Luca F Bricks comparing percutaneous with intradermal BCG vaccine where he reviewed literatures published 1987 to 2002, found that BCG by intradermal route more efficient in stimulating IF-G production by Th-1 lymphocyte **(**the most critical populations of immune cells to confer protection against mycobacterium TB**)** than percutaneous route, he recommended intradermal BCG vaccination [35] .In comparison, a recent randomized trial 2008 in South Africa by Anthony H….et al where they compare incidence of TB in 2 years in 1860 newborn infants vaccinated at birth with intradermal or percutaneous ,they found no significant difference in incidence of TB in both routes of administration.[36]

The previous findings are questionable by another study done by Power CA….et al 1998 where he claimed that mycobacterial dose define the nature of immune response independent of whether immunization is administrated by Intravenous or subcutaneous or intradermal route of administration. [22]

Although relative efficacies with different routes of BCG administration are all debated, but along with recommendation of WHO, intradermal administration of BCG is still commonly used, and till now considered the only method advocated by WHO in comparison with other routes.[17]

In spite of all the debate regarding vaccine efficacy against pulmonary TB, it generally agreed that the vaccine is effective in disseminated disease and meningitis in childhood TB [3][11][24][37][38] ,results of meta- analysis research of BCG efficacy in1994 are shown: [39]

Efficacy of BCG vaccine	
Protection against Disseminated TB	80%
Protection against DEATH from TB	70%
Protection against TB Meningitis	65%
Protection against TB Infection	50%

In another meta-analysis assessed by B Bourd ….et al in 2006 about the effect of BCG vaccine on childhood tuberculous Meningitis and Miliary TB and assessment of cost effectiveness of the vaccine, they estimated that the 100.5 million BCG vaccination given to infants in 2002 would have prevented 29729 cases of tuberculous meningitis in children during their first 5 years or one case for every 3435 vaccinations and 11486 cases of miliary tuberculosis, or one case for every 9314 vaccinations the number of cases prevented would be highest in South East Asia (46%) Sub-Saharan Africa 27% the Western Pacific region 15% and where the risk of tuberculosis infection and vaccine converge also highest. [40]

So it's one of the vaccine recommended for the children in Expanded programme of immunization (EPI)sponsored by WHO which incorporated in it 1974 to strengthen the fight against children TB in developing countries. [2][4][19] [41]

Effect of the prior BCG vaccination on tuberculin test:

Previous BCG vaccine did not affect the utility of subsequent Monteux testing (Tuberculin skin test) in that individual , the Mantoux reaction after BCG vaccine is generally small and unlikely to have indurations exceed 10 mm when vaccination is given in early life [24][42] , furthermore there is progressive weaning of the induration within several years of vaccination . Study done by Nemir RL….et al in France 1983 revealed that tuberculin reactions after BCG were rarely large and they persisted for no more than 5 years[43] , as yet there is no totally reliable method for distinguishing a tuberculin reaction caused by BCG from that due to mycobacterial TB. [15][24][44]

So interpretation of TST is highly dependent on the population of the children being tested [24] ,if the child at high risk of infection, so any reading > 5mm should be considered positive reaction, for those assessed to be at medium risk, 10 mm or greater is considered positive, if the child is unlikely to be infected with mycobacterial TB, a reaction of >15 mm is generally considered positive.[24]

Tuberculin skin test (Monteux test) and risk of T.B infection : [24]

High risk: positive > 5 mm.

- Close contact of infectious adult.

Medium risk: positive > 10 mm.

- Overseas born from high TB prevalence regions.
- Socially deprived ethnic or racial minorities.
- Other locally identified high risk populations.
- Infant and young children (< 4 year)

Low risk: positive > 15 mm

No risk is identified. [24]

Methods of administration of BCG and schedules of vaccination :

Different routes of BCG administration are used for vaccine delivery:

- Intradermal. [17]
- Percutaneous puncture of BCG exposed skin by multipore device. [15]
- Oral route. [15] [45]
- Inhalational route. [46] [47][48]
- Rectally. [49]

The preferred route of administration of BCG vaccine is intradermal [17] injection at low insertion of deltoid [15][17] by syringe and needle ,because it's the only method that permits accurate measurement of an individual dose[7][15].Multiple puncture technique is popular because its easy but reported results are consistently inferior to those obtained with intradermal injection[15] .Oral vaccination, the original method of administration has been largely abandoned because of poor results [15] .Inhalational route **(**inhaled dry powder vaccine **)** solves some problems associated with injectable BCG vaccine , as its stable and can be transported without refrigerator, also doesn't need source of water to reconstitute the vaccine ,traditional BCG vaccine is freeze-dried requiring refrigerated storage(2-8c)during transportation, another advantage is that its administration as easy as breathing that makes it ideally in developing countries in decreasing risk of complications associated with injection, in addition to this ,its route of administration is much closer to the route of infection, but its efficacy and its side effects still under trial as well as rectal route[46][47][49] . Dose of vaccine is about 10^6 cultural particles [15] and it should not be given at the sites where lymphatic drainage makes subsequent lymphadenitis difficult to diagnosis and dangerous **(**especially buttock where lymphatics drain into aortic lymph node) [50]

Recommended vaccine schedule vary widely among countries, the official recommendation of WHO is a single dose administration during infancy to all children from endemic area [17] ,irrespective of HIV exposure unless child has symptomatic HIV disease [51] ,repeated inoculation is of no documented value [17] ,but in some countries repeat vaccination is universal and in others it's based on either tuberculin skin testing or the absence of atypical scar. [25]

United state policy: has never used mass immunization BCG relying instead on the detection and treatment of latent cases. [24]

Libya: immunization of BCG vaccine given to all infants, one dose at birth.

United kingdom: since 1953 and until 2005, UK policy was to immunize all school children at age of 13 years and all neonates born into high risk groups (one dose) , at 2005, the school BCG immunization program was stopped following continued decline in TB rates in the UK population ,the new immunization schedule is based on risk assessment, that involves targeted immunization of neonates and others of high risks. [25]

The uses of BCG vaccine:

Although the use of BCG vaccine for control of TB has been waned, but in recent years the incidence of TB is increasing [15] .Last surveillance data by WHO reveals that in 2006, there were 9 million new cases and about 2 million deaths from TB, that may result from remarkable increase in the rate of multidrug resistant TB [15][17] **(**defined as infection with organism that is resistant to isoniazid and rifampicin with or without resistance to other anti-TB drugs)[52] and destructive impact of TB/HIV co-infection, [15][17]since the description of AIDS in 1981 the world witnessed major changes in the epidemiology of TB , the incidence rate of TB reported globally especially in young children have progressively increased [53] ,so that interest in BCG renewed , 100 million children are vaccinated every year **(**WHO 2008) [4][17] and new insights obtained into their mode of action incorporate it in other uses:-

Cancer chemotherapy: since late 1980, it has been used for treatment of superficial forms of bladder cancer, also used as immunotherapy in colorectal carcinoma, [54] lung cancer, melanoma. [25]

- D.M type I: it is used to induce production of TNF-alpha which can kill T cells responsible for type 1Diabetis mellitus. [55]
- It is used in treatment of chronic inflammatory bladder problem e .g interstitial cystitis, painful bladder syndrome by instillation it directly into the bladder. [25]
- Vaccine is effective against other mycobacterial diseases in particular leprosy, [56] ,now at least 3 countries recommended BCG for contact of leprosy patient. WHO noticed that widespread application of BCG is likely to have been effective in decline of leprosy incidence observed in certain population .Its interested that prospective trial of childhood immunization in Malawi found BCG to be protective against leprosy but not tuberculosis. [57]

- Others, in multiple sclerosis, Parkinson's disease but not commonly used. [58][59]

Contraindication of BCG vaccine:

Except in neonatal period , tuberculin skin test **(**TST**)** should always be done before administrating BCG vaccine [15] a positive test is one of contraindication for vaccination ,because risk of sever local inflammation and scarring is high. [25]

Other contra indications are:

i. Neonate in household where an active TB cases is suspected or confirmed. [25]

ii. Immunosuppression :BCG vaccination should not be given to the person who are immune-compromised either congenital or acquired e. g BCG is absolute contraindication in symptomatic HIV individual **(**lack of knowledge of mother status should not delay vaccination**)** or to those who are likely to become immune suppressed e. g persons who are candidate for organ transplant or chemotherapy[17][25]including X. irradiation. [60]

iii. Those with family history of primary immunodeficiency e. g inherited severe combined immunodeficiency or chronic granulomatous disease until evolution is complete. [25]

iv. Those who have allergy to any component of the vaccine, or have history of anaphylactic or allergic reaction to previous dose of BCG vaccine are contraindication to vaccination.

v. Those with pyrexia >38c. [60]

vi. Those with generalized infected dermatitis, the effect of BCG may be exaggerated in these patients and more generalized infection is possible , so if the child has eczema ,the vaccination site should be away from the lesions and eczema is not contraindication of vaccination. [60]

vii. Pregnancy. [17]

Complication of BCG vaccination (BCG vaccine Disease)

Although immunization against tuberculosis theoretically would be tremendous boon to humanity, but in practice its has been fraught with great difficulties, various strains of mycobacteria used, lack of standardization of vaccine growth and preparation, its role in preventing infection form of TB (Pulmonary TB) is still debated, its reactivity to tuberculin test that occur after vaccination may interfere with management of person who is possibly infected with mycobacterial TB , and also pre BCG tuberculin testing to avoid possible complication ,especially in immune-compromised individual , but it has been very impractical in mass immunization program.

Since TB is still an important public health problem in the world, relative side effects should be accepted, on other hand, if TB is no longer a significant threat, efforts should be made to avoid any annoying consequence of BCG vaccination, no matter how minimal they be .Generally BCG has low incidence of serious adverse reactions and considered as quiet safe, [3][4][5][45]provided that correct immunization techniques are used and those to be vaccinated are probably selected. The normal cutaneous reactions at inoculation site after receiving BCG vaccine can be summarized as:

1. Induration to formation of small papule which usually appear in most infants within 2 or more weeks after vaccination.
2. Papule may increase in size few weeks later (up to 10 mm in diameter).
3. This subside gradually, followed by local lesion that may ulcerate 6-8 weeks later, heals spontaneously leaving a small flat scar 3-6 months[50] ,characteristic raised scar of BCG immunization often used as proof of immunization. [25]

Sever injection site reactions like discharging ulcer or local abscesses formation may be seen, usually as a result of improper injection technique when vaccine is given into subcutaneous layer of skin [61] or as a result of excess dosage of vaccine or vaccinating individuals who are tuberculin skin test positive [25] .Regional lymphadenitis frequently seen in ipsilateral lymph node , axillary, supraclavicular or cervical groups, [2][3][4][5] in the immune compromised host; namely child with HIV or primary immunodeficiency is prone to serious BCG complication **(**disseminated

BCG-it is) [4][37][51] ,the outcome of such condition is frequently fatal, in era before HIV , the reported frequency of disseminated disease was extremely low 0.19-2 case/ 1 million vaccinated infant. [11][37]

Systemic or disseminated BCG disease can be defined when all three of the following conditions are met:

i. Isolation of mycobacteria on culture.

ii. Dissemination evidence by either positive result of blood or bone marrow culture or evidence of infection at > 2 anatomical sites beyond the region of vaccination.

iii. Typical manifestations include weight loss, anemia, hepato-splenomegaly, lymphadenopathy and death. [37]

Systemic complaints such as fever, convulsion, loss of appetite and irritability are extraordinary rare after BCG vaccination. [7]

Classification of BCG disease following BCG vaccination :[37]

Category	Description
i. Regional disease	Persistent ulcer, abscess, sinus or lymphadenopathy limited to the region of inoculation.
ii. Extra regional (localized disease)	Infection of a single anatomic site such osteitis or cutaneous abscess outside the region of inoculation.
iii. Disseminated disease	As mentioned above.
iv. Other BCG disease	In which bacteria are not identified such as uveitis, conjunctivitis, erythema nodosum, keloid formation, these conditions may be immune based.

Another classification of BCG disease:

i. Infectious: include persistent ulcer abscess suppurative and non-suppurative lymphadenitis, osteits, osteomyelitis, arthritis, disseminated BCG-itis.

ii. Non infectious: usually manifests as hypersensitivity reaction e. g erythema nodosum , phlyctenular conjunctivitis, keloid scarring.[61]

Local hypersensitivity reactions occur within few days of vaccination, but generalized one usually occurred following BCG installation into bladder in urinary bladder disease, keloid is commonest of late non infectious complication. [61]

BCG lymphadenitis:

Risk factors :

BCG adenitis occurs with varying frequency in different countries depending on:

A. Factors related to host.
B. Factors related to the vaccine.

A) **Host related factors**:

i. **Age of the child**: the younger the age the increment of risk. [62][13][2] [3][4]

ii. **Immunological status of child**: severe immunodeficiency status of the child either congenital or acquired are associated with increasing risk of local as well as systemic complications after vaccination. [3][4]

iii. **Characteristics of recipient population**: this may explain the difference in the incidence of adverse reaction seen after BCG vaccination in different countries e .g Keloid formation and racial groups. [4]

B) **Vaccine related factors**:

i. **Viability (**the proportion of living and dead bacilli**) :**

After processing, the final product of the vaccine filed in container according to a standard bacterial mass which is estimated by weight or opacity. The extent of local reactions is proportional to total bacterial mass [63] .In a retrospective study on BCG complication in 6 countries in Europe Lotte ..et al concluded that number of viable unit injected has important influence on increasing risk of regional complications. [64]

ii. **Residual virulence of BCG strains:**

Smith…et al, animal immunogenicity study showed that Glasxo 1077 and Tokyo 172 are weak strains ,whereas Pasteur and Danish 1331 are strong strains [11][65] ,in a study done in Hong Kong about risk of post BCG complication showed 0.514/10.000 infants who received the Pasteur strain compared with none of 81304 infants who received Glasxo strain [63] ,similarly Hooi ..et al reported a series of 638 BCG related lymphadenitis in infants due to change in vaccine

strain [66] ,among those BCG strains Pasteur and Copenhagen strains are associated with high incidence of post BCG suppurative adenitis and Tokyo 172 registered as an international reference strain in 1995 by WHO. [4]

iii. **Dose of vaccine given:**

Study by Glud J….et al that investigated suppurative adenitis after intradermal injection of BCG in newborn revealed that frequency of enlarged node or local skin ulceration after BCG vaccine was dose related , the researcher found that low dose was associated with significantly lower rate of suppurative lymphadenitis and skin ulceration after vaccine [67], similarly lotte….et al reported that incidence of 0.1/1000 of this complication in Hong Kong where due to low dose of Glasxo strain given to newborn infants compared with 38/1000 in mass BCG immunization in Algeria where infants received high dose (0.1 ml) of the same strain[45] , similarly when Gothenburg strain was replaced by Copenhagen 1331 strain in Federal Republic of Germany in 1995 there was immediate rise to 1.5% in suppurative adenitis and this fell to 0.02 after dose- response relationship was investigated and dose subsequently lowered.[68]

iv. **Route and technique of administration:**

The mode of administration and skills of a person who gives the intradermal vaccine has been found a significant determinant of the risk, failure of intradermal injection may result in inadvertent subcutaneous administration , which contribute to increase complications rate. In Egypt it was reported that ,10% of vaccinated in public health Welfare clinic exhibit adenitis that need treatment compared with 0.02% of those whom received BCG vaccine in the chest clinic where it was administrated under strict medical supervision[69] .Gheorghin M….et al reported results from Toga in which incidence of non suppurative adenitis was 43% among newborns who received Pasteur 1173 vaccine , upon introduction of good injection technique , the incidence of adenitis caused by Pasteur strain fell to 0.44% [70].

In study by W Daoud in 2003 showed that outbreaks of BCG complications occurred in Gaza, where 225 out of total 6145 newborn infants in the study developed BCG complication, with a rate of 36.61/1000 vaccination and common complication were regional adenitis in 138(61. 33%) of infants, in second follow up study which included 6877 newborn infants the BCG complications occurred at a rate of 6,25/1000

vaccination, which significantly lower than during initial out breaks ,this was due to change of BCG strain and intensive course training for nurses involved in administration of vaccine and strict intradermal injection.[71]

Other factor may contribute to development of BCG lymphadenitis include secondary invasion of immunization site by secondary pyogenic infection. [4]

Clinical features and diagnosis of BCG lymphadenitis:

Recognition of the condition is a little bit difficult ,because in more usual circumstance when attending physician is seeing the child for the first time such a diagnosis may not be obvious, difficulty is due to:-

i. Delayed onset of symptoms usually 2-6 months after vaccination and may be delayed up to 18 months or more as mentioned before.[2]
ii. Absence of the usual immediate vaccine complications.
iii. Absence of systemic constitutional symptoms. [4]
iv. The parent will be unable to relate the presenting symptom of axillary mass with long past history of BCG vaccination and will not volunteer such information unless specially asked for.

On other hand, another difficulty in differentiation of BCG related reactions from lymphadenitis or abscess formation secondary to acute pyogenic infection or rarely due to chronic tuberculous or non tuberculous mycobacterium, although the latter two conditions are cold rather than hot in presentation i. e cold abscess, in addition isolated axillary tuberculous lymphadenitis is extremely rare. [5]

The following features may point to BCG lymphadenitis as etiology:

1. History of vaccination on the same side.
2. Onset usually within 2-6 months, but may be later.
3. Absence of fever and other constitutional symptoms.
4. Absence or minimal tenderness on the lesion.
5. > 95% of axillary ipsilateral lymph node in isolation or in association with others.
6. 1-2 discrete lymph nodes and the involved lymph node are rarely matted together.

So diagnosis mainly clinically based [4] [12] [14] ,if the condition fulfill the criteria mentioned above, this usually sufficient for making the diagnosis in majority of the

cases, investigations add a little for diagnosis[4] , hematological analysis, Chest radiography , tuberculin test have a limited role in the diagnosis except in disseminated BCG disease in immune compromised host, who should have other suggestive symptoms and signs ,and superadded infection of node or in atypical presentation of BCG lymphadenitis where they present as isolated cervical lymph node without concomitant axially lymph node involvement.

So tuberculin test supplement with negative interferon gamma release assay (IGRA) for mycobacterium tuberculosis together with normal CX-ray might help in diagnosis by excluding TB in such rare condition [3] ,in typical presentation of BCG lymphadenitis tuberculin test expected to be positive after recent BCG vaccination and may not be much helpful in differentiate the positively in the reaction caused by mycobacterium TB or mycobacterium bovis .

CX-ray should be normal in all cases of BCG lymphadenitis [3] and any abnormality e. g pulmonary infiltration , opacity may suggestive intrathoracic lymph node enlargement and need further evaluation to exclude TB or disseminated BCG disease.

Cytopathology aspirate from involved lymph node is not very different from that seen in tuberculous lymphadenitis [4,] lymph nodes show epitheloid granuloma with giant cells and restricted centrally located narcosis ,few or absent bacilli in immune-competent host, large satellite caseous abscess without giant cells and numerous bacilli seen in immune compromised patient ,although microbiological confirmation is not generally needed, definitive identification of the bacilli isolated by appropriate culture requires phage typing or mycobacterial gene analysis [72].The conventional polymerase chain reaction (PCR) test for mycobacterial tuberculosis complex is not specific enough to differentiate mycobacterium TB from mycobacterium bovis. [3] Isolation of pyogenic bacteria from aspirate has been reported in many studies although exact significance of this finding is not precisely known .

Treatment of BCG lymphadenitis

Treatment of BCG lymph adenitis has remained controversy, reported treatment varies from doing nothing, only observation, to medical management or use of fine needle aspiration(FNA), to a wide debate about surgical intervention.

Medical treatment

Use of oral erythromycin or anti-tuberculous drugs like isoniazid (INH) ,rifampicin has been evaluated in different studies ,recent results show that use of anti-tuberculous treatment (ATT) neither prevent suppuration nor hasten recovery[13][14][73][74][75][76] in addition to risk of drug side effects .

Fine needle aspiration(FNA)

Preference use of FNA in cases complicated with fluctuant adenitis is advocated by many authors to prevent spontaneous rupture, prolonged discharge and sinus [5][76][77] formation, another opinion advised for intra-nodal injection of INH after FNA [76] although it is safe procedure but risk of recurrence is still there.

Surgical treatment

Some authors reported that FNA is not alternative to surgical excision if nodes become fluctuant , the excision constitutes a definitive treatment of fluctuant adenitis to prevent development of persisting discharge and sinus formation [73][74][78] ,others see that surgical excision needed only in the failed FNA[3][77] or in cases where suppurative node already drained with sinus [78] however , it requires general anesthesia that may carry risk in young child, also complications of surgical wound e.g infection , seroma .

Addition of ATT after excision is preferred by some authors, although extra benefit from this has been questioned in different series [78] .Simple incision and drainage is another choice for treatment of BCG adenitis, but inadequate evacuation of inflammatory material which may result in persisting discharge. [76][80][81]

Future development of tuberculosis vaccine:

Now a day's many new vaccine for tuberculosis in development and entering into clinical trials ,new candidates include live a attenuated mycobacterium tuberculosis, subunit proteins , recombinant DNA vaccine [7] ,all are aim to provide a strong and long lasting immune response in heterogeneous population.

Chapter 3

Aim of the study

AIMS OF THE STUDY

1) Describe clinical profile of post Bacillus Calmette Guerin lymphadenitis.

2) Assess the clinical course and outcome of Bacillus Calmette Guerin lymphadenitis with conservative approach.

Chapter 4

PAITENTS & METHODS

PATIENTS AND METHODS

study design, study time and place :

We conducted a retrospective study for all children presented with BCG lymphadenitis attending Benghazi Children hospital / infectious clinic from 2005 - 2010, the data collected from medical records in the files.

The study field:

All the patients received a single intradermal injection of **(0.05)** ml of BCG, two strains of BCG administered: in 2005 patients received BCG **SSI Danish 1333** strain &from 2006 till 2010 they received **SII Indian** strain in the first two months of life at left deltoid .

Vaccine was given to infants in maternity hospitals or polyclinics or health care centers.

All the infants with post BCG lymph adenitis were seen by infectious clinic team , **(** the patients who had sign of dissemination or who had family history of TB were excluded **)** and they were followed up regularly to document the course and outcome of BCG lymphadenitis within the study period with conservative management, except for 7 patients (two of them treated by excision of the lymph node under general anesthesia , 4 cases under went incision& drainage and one case received ATT prior referral to our hospital) and in each follow up visit, patients examined carefully and node sizes were measured, and any difference in consistency of these nodes were also documented .

Exclusion criteria:

Patients who had family history of contact with tuberculosis or who had signs of dissemination were excluded from our study.

BCG adenitis was diagnosed based on:

i. : H/O of vaccination on same side.

ii. : Axillary or supra clavicular or cervical lymph node enlargement in association or in isolation.

iii. : Absence of local or systemic signs of inflammation.

Medical records were reviewed for age at presentation, age of vaccination, place of vaccination, interval between vaccination and development of adenitis, site and size of enlarged nodes, family history of TB and immune deficiency (congenital or acquired), also for CBC,ESR and chest radiography.

Statistical analysis:

The data collected and analyzed using SPPS version 11 computer program.

Chapter 5

Results

RESULTS

During the study period (2005-2010) , 89 children seen and followed up in the infectious clinic of Benghazi children hospital with post BCG lymphadenitis.

Fifty three (59.6%) of them were males and 36 (40.4%) were females with male to female ratio 1.47:1. Figure No.1.

Fifty eight out of total (65%) received BCG vaccination in the first 2 months of life; 55/89 (61.8%) vaccinated in the first week of life, one child vaccinated in the 2nd week (1.1%) while 2 children (2.2%) vaccinated after the 3rd week of life. The remaining 31/89 (34.8%) of children their time of vaccination was not known .Table No.1.

The age of the presentation was: 77/89 (86.5%) presented within the first 6 months of life, 3 /89 (3.8%) presented at 10,17 , 24 months respectively, the mean of age at presentation was 4.1(SD -/+ 3.1) months. The remaining 9/89 (10%) of children their age at presentation were not known. Figure No.2

The time interval between the vaccination and the appearance of lymphadenitis was as following: 54/89 (60.7%) had lymph adenitis within an interval of 1-6 months , 1/89 (1.1%) presented within an interval of 7-12 months , and 1/89 (1.1%) presented after one year of vaccination. The remaining 33(37.1%) children their time intervals between vaccination and presentation were not known. Table No.2

The number of lymph nodes affected ranged from 1-3 lymph nodes; the majority of children 80/89 (90%) had single lymph node involvement, while the remaining 9 /89 (10%) children had 2-3 lymph nodes involvement. Table No.3

All the 89 children showed left sided lymph nodes involvement (which was one criteria of the diagnosis); 74/89 (83%) had isolated left axillary lymph node, 5/89 (5.6%) had isolated supraclavicular lymph node , 1 /89(1.1%) had left cervical lymph node. Table No.4and5, figure No.3

Nine children /89 (10.1%) had multiple lymph nodes involvement . Table No.5

The mean of the size of lymph nodes was 2.6cm (SD-/+1.1).

The distribution of affected children according to the type of lymph node pathology was: 48 (54%) had suppurative lymphadenitis and 41 (46%) had non-suppurative lymphadenitis. Table No.6

The range and mean of the time needed for improvement of the lymphadenitis in the suppurative and non-suppurative groups were 1- 17 months and 6.7 respectively in our patients managed conservatively; the mean time of improvement in suppurative group was 6.9 (SD -/+ 4.1) and for non-suppurative group was 6.5 (SD -/+3.5) .One girl, 2 years old with suppurative lymphadenitis improved after 46 months.

We found no correlation between the size of the lymph nodes and time of improvement.

Spontaneous decrease in the size of the lymph nodes and resolution was observed in 82 children (92.1%) ,4 children (4.4%) improved after incision and drainage , 2 children(2.2%) improved after surgical excision and only one child treated with ATT. Table No.7, figure No.4

Chest x-ray was normal in 78/89 children (87.6%), the rest of children the data were not recorded

CBC results were normal in 81/89 children (91.1%) ,8/89 children

(8.9%) had no CBC records.

Sixty children /89 (67.4%) had normal ESR, 5/89 (5.6%) had raised ESR.

Figure No.5 showed the number of children with lymphadenitis /year from 2005-2010.

Forty three children (48.3%) during 6years of study period received BCG vaccine in Gumhouria hospital (the main maternity hospital in Benghazi) as shown in Table No.9 and figure No.6

Table (1): Distribution of children with BCG lymphadenitis in Benghazi children hospital 2005-2010 according to age of vaccination:

Age of vaccination/days	Frequency	Percent%
1-7	55	61.8
8-14	1	1.1
>22	2	2.2
Unknown	31	34.8
Total	89	100%

Distribution of patients with BCG lymphadenitis in Benghazi children hospital 2005-2010 according to age at presentation:

Age of presentation /months	Frequncy	Percent%
1-3	35	39.3
4-6	42	47.1
7-9	0	0
10-12	1	1.1
13-15	0	0
16-18	1	1.1
19-21	0	0
22-24	1	1.1
Unknown	9	10.1
Total	89	100 %

Table (3): Distribution of children with BCG lymphadenitis in Benghazi children hospital 2005-2010 according to time interval between vaccination and appearance of lymphadenitis:

Interval/months	Frequency	Percent%
1-6	54	60.7
7-12	1	1.1
>12	1	1.1
Unknown	33	37.1
Total	89	100%

Table (4): Distribution of children with BCG lymphadenitis in Benghazi children hospital 2005-2010 according to number of lymph node involvement.

Number of lymph node	Frequency	Percent %
1	80	90
2	6	6.7
3	3	3.3
Total	89	100%

Table (5): Distribution of children in Benghazi children hospital 2005-2010 according to the commonest site of lymphadenitis:

Site	Frequency	Percent%
Left axilla *	83	93.3
Left supraclavicular	5	5.6
Left cervical	1	1.1
Total	89	100%

*left axilla in isolated or associated with other lymph nodes

Table (6): Distribution of children with BCG lymphadenitis in Benghazi children hospital 2005-2010 according to sites of involvement:

Site	Frequency	Percent %
Left axilla	74	83.1
Left supraclavicular	5	5.7
Left cervical	1	1.1
Left axilla /pectoralis	2	2.2
Left axilla/supraclaviucular/infraclavicular	3	3.5
Left axilla /supraclavicular	2	2.2
Left axilla /infraclavicular	2	2.2
Total	89	100%

Table (7): Distribution of children with BCG lymphadenitis in Benghazi children hospital 2005-2010 according to types of BCG lymphadenitis:

Type	Frequency	Percent%
Suppurative	48	53.9
Non-suppuratieve	41	46.1
Total	89	100%

Table (8): Distribution of children with BCG lymphadenitis in Benghazi children hospital 2002-2010 according to the clinical course:

Clinical course	Frequency	Percent%
Spontaneous resolution	82	92.2
Incision/drainage	4	4.5
Excision	2	2.2
Antituberculous treatment	1	1.1
Total	89	100%

Table(9): distribution of children with BCG lymphadenitis in Benghazi children hospital 2002-2010 according to place of vaccination

Place	Frequency	Percent%
Gumhouria hospital	43	48.4
Polyclinics	14	15.7
Health care centers	13	14.6
Hospitals outside Benghazi	6	6.7
Unknown	13	14.6
Total	89	100%

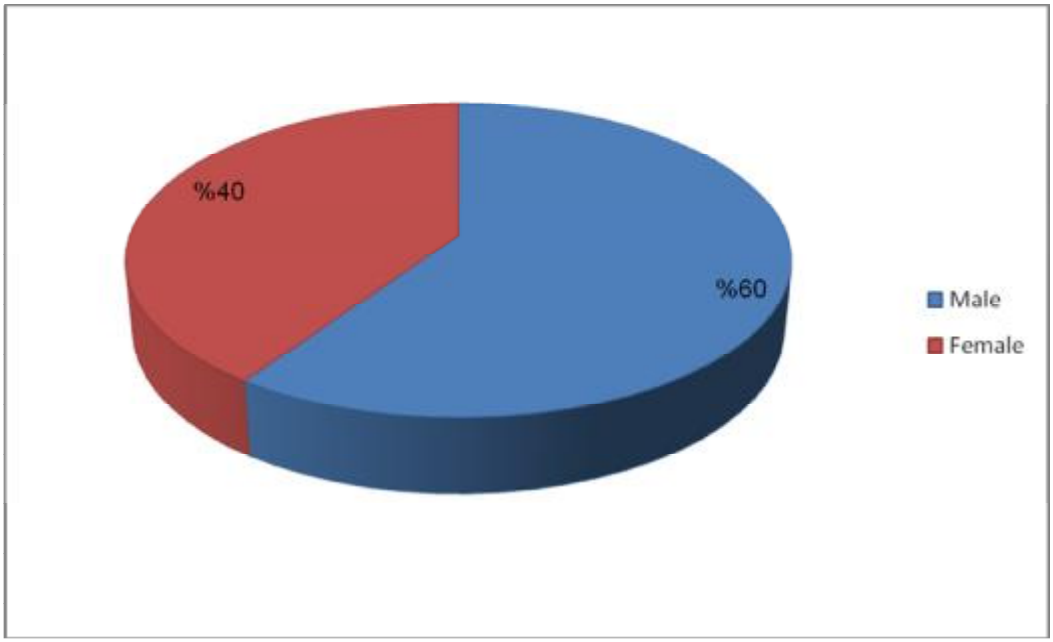


Figure (1): Distribution of cases with BCG lymphadenitis in Benghazi children hospital 2005 -2010 according to sex

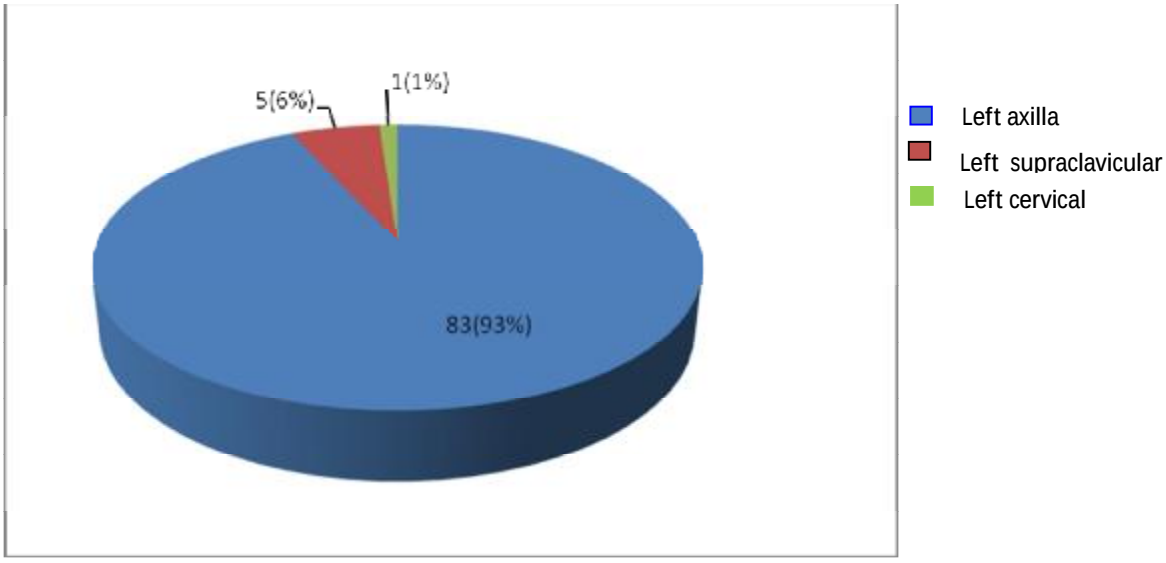


Figure (2): Distribution of cases with BCG lymphadenitis in Benghazi children hospital 2005 -2010 according to commonest site of lymph node involvement.

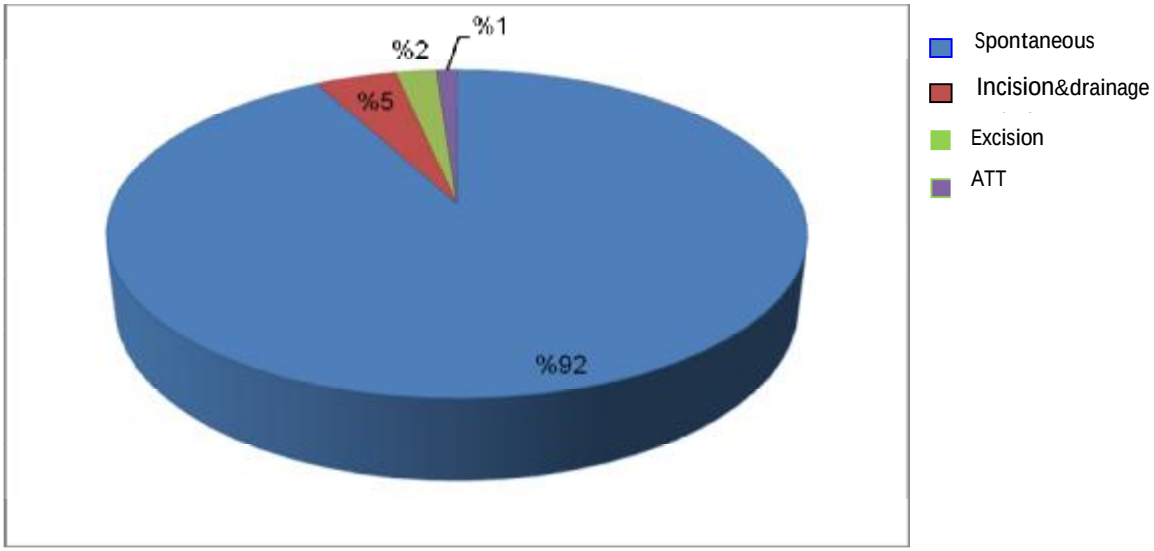


Figure (3) : Distribution of patients in Benghazi children hospital 2005 -2010 according to clinical course of BCG lymphadenitis

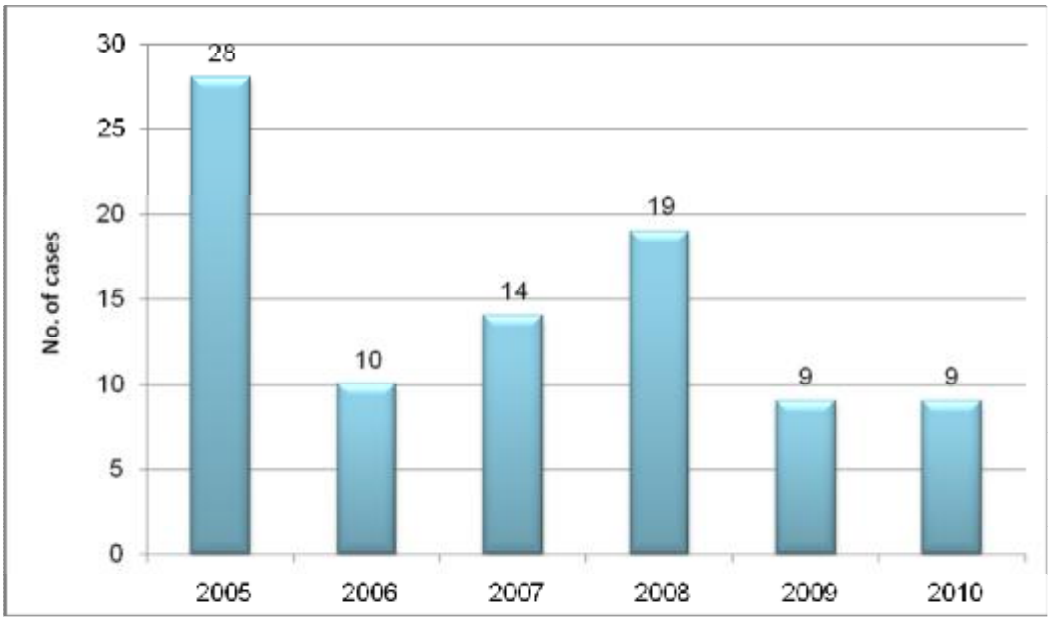


Figure (4): Distribution of patients with BCG lymphadenitis in Benghazi children hospital 2005 -2010 according to number of patients per year

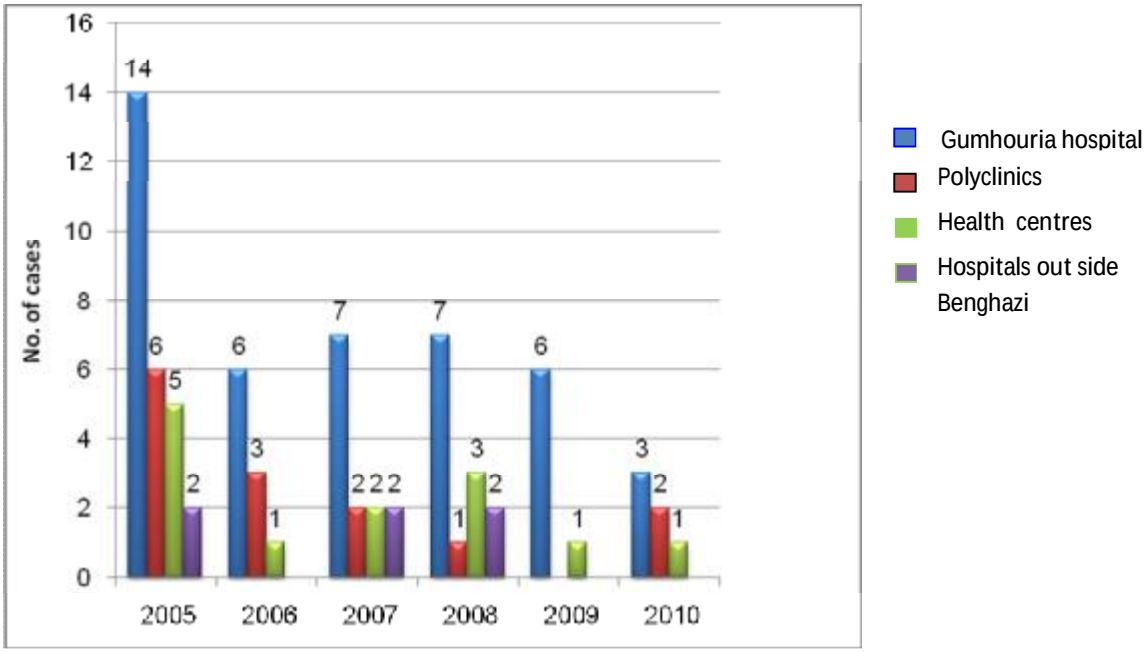


Figure (5): Distribution of patients with BCG lymphadenitis in Benghazi children hospital 2005 – 2010 according to place of vaccination in each year

Chapter 6

Discussion

DISCUSSION

BCG vaccine is a part of immunization program in Libya and is given during neonatal period.

Intradermal vaccination with BCG gives rise a classic primary complex that consists of small nodule at injection site and a small swelling of regional lymph nodes, this is usually self-limiting with no clinical significance and requires no treatment but in small number of children this normal reaction may be exaggerated and results in a large lymph nodes (non-suppurative or suppurative adenitis).

During 6 years of the study period (2005-2010), 89 children presented with post BCG lymph adenitis; all were generally well, none of them had evidence of immune deficiency or history of contact with patient having tuberculosis.

In our study, 60 % of children were males and 40% were females and male to female ratio was 1.47:1 , this observation was also noticed by Bukhari E.. et al from Saudi Arabia ,2012 [62].

Male predominance was also reported by many other authors [45, 41,2] ,while A.B Hamedi.. et al from Iran 2004 ,found more females than males (59.7%) [1].

This study revealed that 65 % children had received BCG vaccine within the first 2 months of life.

Majority of children (86.5%) presented with lymph adenitis within the first 6 months of life , the mean of age of presentation was 4.1months ; this result was similar to that reported by Kheiria M Benghazi 2005 [82]. she found that the age of presentation of the two groups of patients were 5.4 and 5.2 months.

Our result was also similar to that observed by Krishna Kmar .. et al in Malaysia, 2010 [19] and Bukhari E.. et al in Saudia 2012 [62] , and others. [41, 2]

In our study ,60.7% of children developed lymph adenitis within the first 6 months after vaccination ,one case developed adenitis 17 months post vaccination. Zafar Nazir from Pakistan 2005[2] ,found that 92 % of his patients, developed adenitis within 6 months after vaccination, whereas 5 patients developed adenitis1- 5 years after vaccination.[2]

A.B. Hamedi from Iran 2004 ,found that 47% of patients developed adenitis 2-8 months after vaccination.[1]

This delay of presentation of this condition may lead to unnecessary search for a cause and expensive investigations and treatment unless the attending physician is aware of possible late presentation of post BCG lymph adenitis.

Our study revealed that 90% of children had a single lymph node involvement ,the commonest one was the left axillary node (93%) either as isolated or associated with involvement of other lymph nodes ,followed by left supraclaviculur nodes and much less ,cervical lymph nodes ,this was in agreement with findings by Zafer Nazer from Pakistan 2005 [(2)] , Kheiria M ,Libya 2005 (who reported that 91% of patients had left axillary lymph adenitis) [(82)] and others { Bukhari E in Saudi 2012 [(62)] ,WM Chan Hong Kong 2011 [(3)] ,Mustafa in Iran 2008. [(41)] }

In our study, suppurative lymph adenitis was more common than non-suppurative (54% Vs 46 %) ,a finding similar to that reported by Bukhari E[(62)] (60% had suppurative adenitis) , Dommergues M A.. et al from Korea 2009 [(83)] and Jou R.. et al 2009 [(84)] ,while Kheiria found non –suppurative more than suppurative . [(82)]

The time of improvement was defined as the time from development of node enlargement till its regression to less than 1 cm in size ; we observed no significant difference in the time of improvement of both suppurative and non suppurative adenitis (mean 6.9 months Vs 6.5 months) and the mean of time of improvement in both types was 6.7 months in our patients managed conservatively ,these figures were close to that reported by a previous study in Benghazi by Kheiria M 2005 (non-suppurative 5.5 months and suppurative 6.1 months in patients treated conservatively and in the her second group who was treated by ATT ,the mean of time was 5.8 months for non-suppurative and 6 months for suppurative).

A study by A Baki..et al conducted in Turkey 1991,found that the mean of time of improvement in both groups who received ATT and those managed conservatively was 7 months. [(85)]

We found no correlation between the size of lymph nodes and time needed for improvement.

In this study , 82 children (92%) showed spontaneous regression in the size of the lymph nodes ,while 4 children had already underwent incision and drainage of the enlarged lymph nodes when we saw them in our hospital , 2 children treated with excision and one child was on treatment with ATT when we saw him for the first time!.

The most important deferential diagnosis of post BCG lymph adenitis is tuberculosis or disseminated disease, so there is a need for investigations to rule out such possibilities and these laboratory investigations include chest x-ay, CBC and ESR.

In our study, no abnormalities found in the available reports of CBC and chest x-rays and concerning ESR, 5 children had raised values which attributed to upper respiratory tract infection and wheezy chest.

In our study ,the largest number of children with post BCG lymph adenitis was seen in the year 2005 (28 children) we think the cause was due to BCG SSI Danish strain 1331 ,this strain was related to out breaks of BCG lymph adenitis seen in Saudi Arabia , Alrabiah AA 2012 [6] ,Milstien JB 1990 [63] ,and according to Smith D 1997 ,animal immunogenity study, showed that Danish strain more reactogenic [65] ,the other explanation of this number of children in 2005 is that children with lymph adenitis were more referred to our hospital than other years.

Beside the type of strain as a cause for lymph adenitis, the technique may be responsible for a number of cases, especially with the fact that BCG vaccine is available and given in many polyclinic and health care centers, Megahed G M et al 1986 [69] ,W Daoud 2003. [71]

In this study, we were unable to estimate the prevalence or the incidence of post BCG lymph adenitis because not all children with this condition referred to our hospital and clinic.

Chapter 7

Conclusions & Recommendations

CONCLUSION

On the basis of study's results, review of previous literatures and knowledge of advantage and disadvantage of available treatments of BCG lymphadenitis , this study was in accordance with the previous published literatures that :

1- Males are affected more than females.

2- The mean of age of presentation was 4.1months.

3- The most commonly involve lymph node was left axilla.

4- BCG lymphadenitis is associated with high incidence of suppuration .

5 - Eighty two patients (92%) improved without any intervention.

Furthermore, the study conclude that:

BCG lymphadenitis follow a benign course in immunocompetent child with complete spontaneous recovery , assurance and observation are main stay in management of both types of adenitis ,but if the node shows significant enlargement and suppuration with prolonged course that cause concern to the family and frequent wound care is required, so fine needle aspiration may be needed .

RECOMMENDATION

i. Physician should be aware of normal reaction to BCG vaccine to avoid unnecessary investigations and unneeded admissions to the hospital.

ii. Close follow up and assessment of patients with BCG adenitis till resolution of lymphadenitis.

iii. Good nurse training for strict intra dermal vaccine administration is required as a result of fact that many outbreaks of BCG adenitis around the world have declined after intensive course training of nurses for vaccine administration.

iv. Assurance the family.

v. Patients file should be complete and contain clear and correct information.

vi. **Furthermore we recommend that**: immunization program manager should be aware of complications of changing BCG strains and suppliers should get the vaccines from well trusted manufacturers, and more researches have to be conducted to evaluate efficacy of used vaccine .

Chapter 8

Reference

REFERANCES

1 -AB Hamedi, Avelayati .Clinical course study of post BCG vaccination .The journal of infectious disease . 2004 ; 3(2).

2 - Zafer Nazer , Saquib H . BCG lymphadenitis changing trends &management . J Ayub medcottabbottabad 2005 ;17 (4) .

3 - WM Chan , Y W kwan… et al . Management of BCG lymphadenitis .Nk j pediatric 2011 ;16 :85 - 94 .

4 - Goraya JS , Viridi VS . BCG lymphadenitis . Post graduated m j 2002 ;78 : 327 -329 .

5 -Hans Jacob ustvedt . Local reaction in BCG vaccination. Bull world hit 1950 ;2 : 441 – 468 .

6 -Alrabiah AA , Alsubaie SS… et al . Outbreaks of BCG related lymphadenitis in Saudi Arabia at university hospital after a change in the strain of vaccine .Ann Saudi med 2012 ; 32 (1): 4 - 8 .

7 - Robert M kliegman , Richard E Behrman …et al . Nelson text book of pediatrics. 18th edition , chapter 212 ;1253 .

8 - Lulu Ahamed A . Pathological finding for BCG infection in immunocompetent &immunocompromised patients . Amj clin pathology 2000 ;113 :703 -708 .

9 - Harry L Joachim's , L Jeffrey Medeiros .Joachim's lymph node pathology , first edition , p :130-134 .

10 - B Bhandari , R Kurana… et al . Management of post BCG lymphadenitis . Indian J pediatr1980 ; 47: 367 -370 .

11 -Fine PEM , Carneiro …et al . Issues relating to use of BCG immunization program – a discussion document .WHO document . WHO / v&b /99.23 Geneva ; 1999 :WHO .

12 -Helmic CG , Dsouza AJ…et al . An outbreaks of sever BCG lymphadenitis in saint lucia,1982-1983.West indies med j 1986 ; 35:7-12 .

13- Coglayan S ,Yegin O …et al . Is medical therapy effective for regional lymphadenitis following BCG vaccination .AMJ dis Child 1987 ;141 :1213 -4 .

14 -Kuyucu N , Kuyuc S…et al . Comparison of erythromycin ,local administration & placebo therapy for non suppurative BCG adenitis . Pediatr infect dis j . 1998 ;17 .

15- Ralph D feign , Jame D Cherry . Text book of pediatric infections1992 Volume (2) ,third edition ,chapter 130 , P :1352 -1354 .

16- Lagranderie MR , Balazuc AM… et al . Comparison of immune response of mice immunized with different mycobacterium bovis BCG vaccine strain .Infect immun.1996 ; 64 (1) :1-9 .

17- BCG vaccine .WHO position paper .Wkly epidemiological records 2004; 79:27 - 38.

18- Kroger L , Brander E …et al . Osteitis caused by BCG vaccination : a retrospective analysis of 222 cases . Ped infect j .1994 ;13 :(2) : 113 - 6 .

19 - Kirnishna KG , Freg YC . BCG adenitis –need for increased awareness. Malaysia j med SCI . 2011 ;18 (2) : 66 -69 .

20- Virgina Davids , Willem H …et al . Dose dependent immune response to mycobacterium bovis BCG vaccination in neonate . Clin vaccine immunol 2007 ;14(2) :198 – 200 .

21 - Mori T, Yamauchi X…et al . Lymph node swelling due to BCG vaccination with multipicture method . Tubercle lung dis 1996 ;77 :269 -73 .

22- Power CA , Weig … et al . Mycobacterial dose define the TH1 /TH 2 nature of immune response independent of weather is administrated by intravenous, subcuteanous or intradermal route .Infect immune 1998; (12) :5743 – 50 .

23- B Sanyal . Lecture notes on microbiology and immunology for dental students 1998 , chapter 31 , p:121 .

24- David Isaacs , E R Chard Moxon . A practical approach to pediatric infection 1996 , first edition , chapter 1B.9 ,18 , p:162-165 , 557 -558.

25 - http://en.wikipedia.org/wiki/Bacillus_Calmette%E2%80%93Gu%C3%A9rin

26- Rosenthal SR …et al . BCG vaccination against TB in Chicago: a twenty year study statistically analyzed : Pediatrics 1961 ;28 :622 .

27- Palmer CE , Shaw LW . Community trail of BCG vaccination .Am rev tubercle 1958 ;77:877 .

28 - British thoracic and tuberculosis association (BTTA) research committee . BCG vaccination by multiple puncture : 4th report .Tubercl 1971 ;52 :19 -30 .

29- Tuberculosis prevention trails "trail of BCG vaccine in south India for TB prevention" . Bulletin of WHO 1979 ; 57 (5) 819 -827.

30- Pake GE , Innes JA . Protective effect of BCG vaccination in Asian infant . A case control study . Archives of disease in childhood 1988 ;63 (3) :277 -281 .

31- Brandt , Feino CJ… et al . Failure of mycobacterium bovis vaccine :some spices of environmental mycobacterium block multiplication of BCG and induction of protective immunity to TB . Infect immn 2000 ;(2): 672 -78 .

32- Rook GAW , Dheda K …et al . Do successful TB vaccine need to be immunoregulatory rather than merely TH1 –boosting ? .Vaccine 2005 ; 23 (18) :2115 – 20 .

33- Jeevan A , Shama AK …et al . Ultraviolet radiation reduce resistance to mycobacterium TB infection in BCG –vaccinated guinea pigs .Tuberculosis 2009 ;89 (6):431 -8 .

34- Vaughan JP , Menu JP…et al . Percutenous BCG immunization trail using WHO bifurcated needle . j trop med hyg 1973 ;76 :143 -6 .

35- Luca f Brick . Percutenous or intradermal BCG vaccine ? . J pediatric (RIO) 2004 ;80 :93 -8.

36- Anthony Hawkridge , Mark Hatheri …et al . Efficacy of percutenous versus intradermal BCG in the prevention of tuberculosis in South African infants: Randomized trail BMJ. 2008 ; 337: 92052 .

37- Talbot EA , Perfins MD . Disseminated BCG disease after vaccination . Clinical infectious disease 1997;24 :1139 – 1146 .

38- Bannon MJ . BCG and tuberculosis .Arch dis child 1999 ; 80 :80-3 .

39- Goldiz G , Brewer T …et al . Efficacy of BCG vaccine in prevention of TB: meta-analysis of published literature .JAMA 1994 ; 271 :698 -702

40- B Bourd , PEM fine …et al . Effect of BCG vaccination on childhood tuberculous meningitis and military TB worldwide ; A meta –analysis and assessment of cost effectiveness . lancet 2006 ; 367 :1173 .

41- Mostafa B , Jamshid A . Post BCG lymphadenitis in vaccinated infants in Yazd , Iran j pediatr 2008 ;18 (4):351 -356 .

42- Menzie R . Effect of BCG vaccination on tuberculosis reactivity . Am rev resir dis 1992 ;145 :621 - 625 .

43- Nemir RL , Teachner A . Management of tuberculin receptors in children &adolescents previously vaccinated BCG . Pediatri infect dis .1983 ; 2 :446 -451 .

44- Fox AS , Lepow ML . Tuberculin skin testing in Vietnamese refugees with a history of BCG vaccination . Am j dis child 1983 ; 137 : 1093 -1094 .

45- Lotte A… et al . BCG complications . Estimate of risks among vaccinated subjects & statical analysis of their main characteristic . Advance in TB research 1984; 21 : 107 -193 .

46- Www. Pharmainf .net / namanm / inhaled_tubeculosis – vaccination.

47-http://books.google.com.ly/books/about/Engineering_a_New_Tuberculosis_Vaccine_f.html?id=Vlxm1Vy4QMwC&redir_esc=y.

48- http://www.hsph.harvard.edu/news/magazine/infectious-diseases/spr08tbvaccine/

49- Lagranderie MR , Balazuc AM …et al . Development of mixed TH1/ TH 2 type immune response &protection against mycobacterium TB after rectal or subcutaneous immunization of newborn ,adult mice with mycobacterium bovis BCG. Scandinavian journal of immunology . 2000 ; 55(3) :293 – 303

50- WWW.Kiros2.com/78_BCG lymphadenitis.

51- Hasseling AC , Schaaf HS …et al . Danish BCG induced disease in HIV infected children .Clin infect dis . 2003 ; 37:1226 -33 .

52- Iseman MD . Treatment of multi drug resistance TB . Neng j med 1998 ;329 :784.

53- Maher D , Ravilione M . Global epidemiology of TB .Clin chest med 2005 ;26 :167.

54- Mosolits S , Nilsson B…et al . Toward therapeutic vaccine for colorectal ca :a review of clinical trail . Expert rev vaccines 2005 ;4 (3):329 – 50 .

55- Human trail to begin on "diabetic cure " after terminology ill mice are returned to health . Daily mail (London) 2008 .

56- Zodepey SP . Protective effect of BCG vaccine in the prevention of leprosy :a meta-analysis , Indian j dermato venerelleprol . 2007 .73 :86- 93 .

57- Ponnighaus JM , Fine PEM…et al . Efficacy of BCG vaccine against leprosy &TB in northern Malawi .Lancet 1992 ;339 :636 – 639 .

58- Ratschmann OT , Mccrory DC… et al . Immunization panel of multiple sclerosis council for clinical practice gu idline . Neurology 2002 ;59 (12) :1837- 43

59- Ristori G , Buzzi MG…et al .Use of BCG in multiple sclerosis . Neurology 1999 ;53 (7) :1588 – 9 .

60- Www . Immunisation .i.e. /en /… /PDF file_14990_en. PDF .

61- JM Grange . Complications of BCG vaccination and immunotherapy and management . Communicable disease & public health 1998 ; 1(2) : 84 -8 .

62- Bukhari E , Alzahrari M ..et al .BCG lymphadenitis : a6 years experience in two Saudi hospitals .Indian j pathol microbiol 2012 ;55 :202 – 5 .

63- Milstein JB , Gibson JJ . Quality control of BCG by WHO : a review of factors may influence vaccine effectiveness & safety . Bull world health organ 1990 ;68 :43 -108.

64- Lotte A…et al . Second (IUATLD) study on complications induced by intradermal BCG vaccination . Bull int union tuberc lung dis 1988 ; 2 :63: 47 - 59 .

65- Smith D , Harding C…et al . Potency of BCG vaccine as evaluated by their influence in bacillem Smart scan Local disc scenic phase of experimental airborne TB in guinea pigs . J boil stand . 1997 ;7 (3): 179 – 197 .

66- Hooi LN , Athiyah SO , An outbreaks of BCG related lymphadenitis in Malaysian infants . Med j Malaysia 1994 ; 49 (4):327 -335 .

67- Glud J , Mangnus K …et al . Suppurative lymphadenitis following intradermal BCG in newborn : a preliminary report . Bmj 1955 ; 1048 - 54 .

68- Brehumer W…et al . Regional suppurative adenitis following BCG . Dutch medizins chwochechrift 1977 ;35 :1251 -1255 .(Summary)

69- Megahed GM , Mohoud ME . Axillary lymphadenitis after BCG vaccination . Developments in biological standardization 1986 ; 58 : 33

70- Gheorghin M …et al . Potency and suppurative adenitis in BCG vaccination . Development in biological standardization 1978 ; 41 : 79 -84 .

71- W Daoud .Control of outbreaks of BCG complication ,Gaza . Respirology 2003;8:376-78

72- Yan JJ , Chen FF… et al . Differnation of BCG induced lymphadenitis from TB in lymph node biopsy specimen by molecular analysis of pen A & oxy r . J path 1998 ;184 :96 – 102 .

73- Aggarwal NP , Kallan BM …et al . Clinico-excisional study of lymphadenitis following BCG vaccination .Indian j pediatric .1990 ; 57: 585 - 6.

74- Merry C , Fitzgerald RJ . Regional lymphadenitis following BCG vaccination . pediatric sug int 1996 ;11 : 269 -71 .

75- Close GC , Nasiro R . Mangement of BCG adenitis in infancy . J trop pediatri. 1985 ; 31 :286.

76- Noah PK , Pande D…et al . Evaluation of oral erythromycin & local isonazid instillation therapy in infants with BCG lymphadenitis & abscess . Pediatr infect dis j . 1983 ;12 :136 -9 . .

77- Banani SA , Alborzi , Needle aspiration of suppurative post BCG adenitis. Arch dis child 1994 ; 1994 ;71 :446 - 7

78- Hengster P, Solder B…et al . Surgical treatment of BCG lymphadenitis .World j sur 1997 ; 21 : 520 – 3 .

79- Al salam AH , Kothari MR…et al . Safety of intradermal BCG vaccine neonate in eastern Saudi Arabia . Saudi M J . 2012 ; 33 (2):172 - 6.

80- Tam PK , Stroebel AB… et al . Caseating regional lymphadenitis complicating BCG vaccination :a report of 6 cases . Arch dis child . 1982;57 :952 - 4 .

81- Oguz F , Mujgan S…et al . Treatment of BCG lymphadenitis . pediatr infect dis j .1993 ;12 :136 -9 .

82- Khireia M Bugalawi . Therapeutic policy in post BCG lymphadenitis .First medical conference of faculty of medicine ,Benghazi 2005 .

83- Dommergues MA , Deiarocque F …et al . Local and regional adverse reactions to BCG-SSI vaccination : a12 month cohort follow up study . Vaccine 2009 ; 27 : 6967 - 73 .

84- Jou R , Huangu . Tokyo -172 BCG vaccination complication Taiwan .Emerg infect dis 2009 ;15 :1525 – 6 .

85- A Baki , Susta… et al . Therapy of regional lymphadenitis post vaccination Infection 1991 ; 19 (6): 414 – 6.

النتائج المترتبه عن التهابات العقد الليمفاويه بعد تطعيم بي سي جي
في مستشفي الاطفال / بنغازي 2005 - 2010

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تطعيم بي سي جي هو التطعيم المستخدم للوقاية من مرض الدرن الرئوي ,حيث يعطي في الأيام الأولي بعد الولادة , ومن أهم التأثيرات الجانبية لاستخدام هذا التطعيم هو التهاب العقد الليمفاوية والتي بلغت نسبتها في بعض الدراسات الي 98% من المضاعفات , ومضاعفات الأخرى تتمثل في التقرح الجلدي وحدوث خراج في مكان حقن التطعيم .وكذلك التهاب المفاصل والتهاب العظام و أخري نادرة الحدوث.

الغرض من الدراسة:

تطعيم بي سي جي هو أحد التطعيمات المقررة في البرنامج الوطني للتطعيمات ,وبما أن التهاب العقد الليمفاوية هي أهم المضاعفات لهذا التطعيم, ونتيجة لنقص الدراسات في هذه الموضوع في مجتمعنا رأينا بأنه لابد من تسليط الضوء علي الشكل السريري للمرض وكذلك النتائج المترتبة عليه.

طريقة البحث :

دراسة استرجاعية تتضمن مراجعة ملفات المرضي المصابين بالتهابات العقد الليمفاوية من 2005-2010 بعد إحالتهم لعيادة الأمراض السارية بالمستشفي .

خضع المرضى لفحص دوري شامل مع تدوين أي تغيرات تحدث في هذه العقد من حيث استمراريتها و زيادتها في الحجم أو تحولها إلي عقد التهابيه صديدية مع إجراء تحاليل الدم الدورية وصورة الأشعة السينية علي الصدر كإجراء مبدئي واحترازي للمرضي .واستبعد من هذه العينة المرضى اللذين يعانون من أعراض نقص المناعة أو يوجد لديهم تاريخ عائلي يتعلق بمرض الدرن الرئوي .

نتائج البحث:

من نتائج المستخلصة من هذه الدراسة إن نسبه المرض بين الذكور اعلي منها في الإناث بنسبة 60% , وكذلك إن أكثر المرضي في الفترة العمرية بين شهر إلي 6 أشهر (86.5%) من العينة ووجدنا أيضا أن (% 90) من المرضي يعانون التهاب عقده ليمفاويه واحده، و(10%) يعانون من التهابات في 2 إلي 3عقد ليمفاويه وكانت العقد الليمفاوية في منطقه الإبط الأيسر هي أكثر الأماكن إصابة حيث بلغت النسبة إلي % 93.3 ، يليها العقد الليمفاوية في منطقة فوق الترقوة بنسبة 5.6% ومن ثم العقد الليمفاوية العنقية في 1.1% من العينة .

وكذالك وجدنا إن (46%) من المرضي يعانون من التهابات العقد الليمفاوية من النوع البسيط الذي لم يحدث فيه التهابات صديدية و (54%) من المرضي يعانون من التهابات العقدية الصديدية.

ولوحظ ان أكثر حالات الإصابة كانت في سنة 2005 (31.5%) ,كما لوحظ إن أكثر الحالات في جميع سنوات الدراسة قد تلقت تطعيمها في مستشفي الجمهورية(48.3%).

ولقد وجدنا من خلال هذه الدراسة ان نسبة الشفاء التام للمرضي دون أي تدخل جراحي بلغت اكثر من (92%) في كلا النوعين من التهابات العقد الليمفاوية ومتوسط الوقت للشفاء 6.7 شهرا .

الاستنتاجات المستخلصة من هذه الدراسة :

إن التهابات العقد أليمفاويه الناتجة عن تطعيم بي سي جي تتبع مسار حميدي في الأطفال اللذين لا يعانون أي نقص في المناعة حيث إنها تتماثل للشفاء الكامل دون أي تدخل طبي . وإن أهم خطوات العلاج هي طمأنة الأسر ومتابعة المرضي بشكل دوري حتي يتم الشفاء الكامل .

التوصيات

1-لابد آن يكون الطبيب علي دراية برد فعل الجسم الطبيعي للتطعيم حتى لا يتعرض المريض لفحوصات غير لازمه .

2- المتابعة الدوريه للمريض حتى يتم شفاؤه من المرض ومراقبته من أي أعراض جانبيه قد تحدث له.

3-تكثيف تدريب هيئة التمريض علي الطريقة الصحيحة لإعطاء التطعيم تحت الجلد .

4-الدعم المعنوي والتوعوي للأسر بخصوص عدم خطورة هذا المرض عندما يكون تحت إشراف طبي .

5- التأكيد علي ان تكون ملفات المرضي تحتوي علي معلومات واضحة وكاملة وصحيحة .

6- التأكيد علي توصية مسؤولي الإمداد الطبي بضرورة اختيار التطعيم الذي تتوفر فيه الفعالية وقلة التأثيرات الجانبية .

جامعة بنغازي

كلية الطب

النتائج المترتبه عن التهابات العقد الليمفاويه بعد تطعيم بي سي جي في مستشفي الاطفال /بنغازي

2005- 2010

هذه الاطروحة مقدمة كجزء من متطلبات نيل درجة الماجستىر في طب الاطفال

من قبل

هدي مفتاح الشركسي

بكالوريوس طب والجراحة

مشرف البحث

د .خيريه بوجلاوي

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ذي حجة 1433 اكتوبر 2012