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OPEN PEER REVIEW

Disseminated Bacille Calmette-Guérin Vaccine-Induced Disease in a Sample of Iranian Children: A Longitudinal Case-Series Study

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About this report

This open peer review (OPR) report shows the public comments made on this article during peer review, by the reviewers, the associate editor and the editor-in-chief, for every revision round, together with the authors' replies. Comments appear only with the consent of the people who wrote them. Reviewers who chose to sign their report are named; the others are shown as "Referee". Comments are edited for language only, and confidential remarks to the editors are not included.

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1 Original submission

2 comments · 20 Aug 2024 – 30 Aug 2024

Referee 1 Reviewer

MINOR REVISION 20 Aug 2024

Dear Editor
I have read the manuscript. The following comments should be considered by the authors.
1. In the title of the manuscript, "Childe" should be replaced with Children.
2. The study design is a "Case-Series study". The authors could avoid describing it as longitudinal.
3. The authors should provide more details in the methods section of the abstract. The approach to data collection and the source of the data, along with the study setting, should be stated.
4. Table 1 should be revised according to the principles of scientific writing. All variables should be stated in one column.
5. The titles of the tables should be stated at the top of the corresponding tables.
6. In Table 2, what is the rationale for stating the patient number? If it is necessary to report patient numbers or IDs, it is better to number them consecutively starting from one.

Reviewer,

Ali Amanati Reviewer

MINOR REVISION 30 Aug 2024

There are several considerations regarding potential objections to the current form of the manuscript titled "Disseminated Bacille Calmette-Guérin Vaccine-Induced Disease in a Sample of Iranian Children: A Longitudinal Case-Series Study," particularly concerning the results and tables:

- There are no established treatment guidelines for BCG-induced systemic complications. This could lead to objections regarding the treatment protocols used in the study, as different approaches may yield varying outcomes.

- The study discusses various definitions of DBD and BCG osteomyelitis, which may lead to inconsistencies in diagnosis and reporting. Different criteria for defining these conditions can complicate comparisons with other studies and may affect the reliability of the findings.

- The reported mortality rates for children with DBD are high, ranging from 25% to 80%. However, the study does not provide detailed information on the causes of death or the specific circumstances surrounding these cases, which could provide valuable insights into the severity and management of DBD.

- The study indicates that most patients were immunocompromised, but it does not elaborate on the specific types of immunodeficiencies in the cohort. This lack of detail may limit the understanding of how different immunodeficiencies impact the clinical presentation and outcomes of DBD. (Among the patients, 31.8% had severe combined immunodeficiency (SCID), 45.5% had Mendelian susceptibility to mycobacterial diseases (MSMD), and one patient had Wiskott-Aldrich syndrome (WAS). The immunodeficiency type for 18.1% of the patients remained unknown.)

Other shortcomings:
- Table 3: remove the "Additional sign & symptom (probably unrelated to BCG vaccination)" column. This table provides treatment and outcome information, and I suggest moving this heading to Table 2.

- "Molecular technique" should be described in more detail.

> _ The discussion section should start with the study's overall findings.

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Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Dear Editor,

Thanks for your consideration,

Answers to reviwer1 in red:

Comment number 1: Patient number 12 have not compliance for drug consumption. We correct all to most patients. We added the prognosis and outcome of MSMD patients added to outcome part with purple.

Comment number 2: Patient 1 regiment for treatment was (RHEClr) 4 drugs (rifampin, isoniazid, ethambutol, clarithromycin)

Patient number 13: HEClrAMK/IFN-γ also get 4 drugs: isoniazid, ethambutol, clarithromycin and amikacin

In patients 18, and 22 ethambutol were omitted with mistake and we corrected it.

Comment number3: As you know there is not a specific protocol for treatment of DBD, we use presented regimen in our patients and mentioned the prognosis. It is expected that after conducting numerous studies with different treatment regimens, the most appropriate treatment regimen in terms of drug side effects and treatment prognosis will be determined by conducting systematic reviews and metanalysis studies. as mentioned in our references we use the reference number 37 for this treatment

Comment number 4: In older studies, several patients with DBD did not appear to have immunodeficiencies, but due to molecular advances and the recognition of new immunodeficiencies, the number of patients with DBD who do not have known immunodeficiencies is decreasing.

Comment number 5: Considering the occurrence of the DBD at a very young age and the lack of a uniform diagnostic protocol, if the history and examination did not point to HIV disease, considering the social burden, our emphasis was on conducting tests for patients with leukopenia and lymphopenia.

Comment number 6: The reference number 40 was added

Reviewer 2 in blue:

Comment number 1:

The title is: *Disseminated Bacille Calmette-Guérin Vaccine-Induced Disease in a Sample of Iranian Children: A Longitudinal Case-Series Study,"*

Comment number 2: in present study 22 patients with signs and symptoms which was doubtful for DBD were entered and evaluated and fallowed for several years and their outcome evaluated. Because the number of cases is 22 we did not use cohort study and prefer to say longitudinal study. We could omit a case series and write a cohort study. would you please help us for the best word.

Comment number 3: the changes was done in manuscript in blue

Comment number 4: the changes was done in manuscript in blue

Comment number 5: the changes was done in manuscript in blue

Comment number 6: the changes was done in manuscript in blue

Reviewer number 3 in purple:

Comment number 1: As you know there is not a specific protocol for treatment of DBD, we use presented regimen in our patients and mentioned the prognosis. It is expected that after conducting numerous studies with different treatment regimens, the most appropriate treatment regimen in terms of drug side effects and treatment prognosis will be determined by conducting systematic reviews and metanalysis studies. as mentioned in our references we use the reference number 37 for this treatment

Comment number 2: we evaluated the BCG osteomyelitis in different study and omit the BCG osteomyelitis in discussion in present study.

Comment number 3: In our study as mentioned in table all SCID patients died because of sepsis

2 patients with MSMS died one because of poor compliance to treatment and one of them because of multiple organ dysfunction at presentation and poor response to treatment. Our WAS patients died because of bone marrow transplantation complication.

Comment number 4: in table 2 we define our patients immunodeficiency type

Comment 5: Real time PCR was used for detecting mycobacterium tuberculosis complex targeting IS6110 and mpb64 gene

Comment 6: In the present study, 22 children who were taken to one of the two referral pediatric hospitals in Isfahan in a 13-year period were evaluated. Most of the patients were immunocompromised, and the percent for each condition calculated: 26.9% of patients had SCID, 12 patient (38.4%) had MSMD (mainly IL-12Rβ1 deficiency), one patient had Wisckot-Aldrich Syndrome (WAS). The best prognosis was for MSMD patients with 4 drug regiment. Considering the relative prevalence of immunodeficiency diseases, we think that probably several patients with other immunodeficiencies such as SCID died before reaching the diagnosis of DBD. Therefore, this study cannot express the proportion of immune defects in patients with DBD.

This paragraph was added to the first paragraph of discussion.

2 Revision 1

1 comment · 9 Sep 2024

Referee 1 Reviewer

MINOR REVISION 9 Sep 2024

Dear Editor
Unfortunately, it wasn't easy to follow how the authors addressed the comments, as they did not include the comments raised in their detailed response to the reviewers. However, Table 1 should be revised using a scientific approach (Variable, Category, N (%)), e.g., Gender Male 11 (11).
Reviewer,

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Revision 2

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Dear Editor,

Thanks for your consideration

We omit the table 1 and rewrite the data in text (in blue)

Best wishes

3 Revision 2

0 comments

No public comments in this round.