Author's response to reviews

Title: Severe congenital neutropenia caused by the ELANE gene mutation in a Vietnamese boy with misdiagnosis of tuberculosis and autoimmune neutropenia: a case report

Authors:

- Quang Van Vu (vvquang@hpmu.edu.vn)
- Taizo Wada (taizo@staff.kanazawa-u.ac.jp)
- Tham Thi Tran (tttham@hpmu.edu.vn)
- Duc Ngoc Ngo (ngocducbsnt@gmail.com)
- Thuc Van Dinh (dvthuc@hpmu.edu.vn)
- Cuong Hung Nguyen (cuongshpthp@yahoo.com.vn)
- Huong Thi Minh Le (lehuong@mail.ru)
- Akihiro Yachie (yachie@staff.kanazawa-u.ac.jp)
- Sang Ngoc Nguyen (nnsang@hpmu.edu.vn)

Version: 4
Date: 20 October 2014

Author's response to reviews: see over
Dear Editors

Please find a file of “Severe congenital neutropenia caused by the ELANE gene mutation in a Vietnamese boy with misdiagnosis of tuberculosis and autoimmune neutropenia: a case report” by Quang Van Vu, Taizo Wada, Tham Thi Tran, Duc Ngoc Ngo, Thuc Van Dinh, Cuong Hung Nguyen, Huong Thi Minh Le, Akihiro Yachie, and Sang Ngoc Nguyen.

We would also like to thank the referees for their feedback that helped us to improve our manuscript. Our detailed responses (point-by-point response) to editor’s comments and each referees’ comments are described below. In the revised manuscript, we highlighted the revisions in yellow color.

Your consideration of our manuscript is greatly appreciated.

I confirm that all our authors have approved the below changes. Correspondence should be directed to me, at the below address.

Please direct all correspondence about this paper to me following address:

Quang Van Vu, MD, PhD
Department of Pediatrics,
Haiphong Medical University, Vietnam
72 A Nguyen Binh Khiem, Ngo Quyen, Haiphong, Vietnam
Phone: +84-313-733-311
Fax: +84-313-733-315
E-mail: vvquang@hpmu.edu.vn

Thank you for considering our paper. We look forward to receiving your rely.

Sincerely,

Vu Van Quang
Response to Editor’s comments

1. Thank you so much for your comments. We have added line number, and we do not use page break in our manuscript. The sentence: “Our results suggest that patients with chronic severe neutropenia and severe bacterial infections should be considered to genetic analysis for confirming diagnosis of SCN” was cut in both Abstract and the part of conclusion. Genetic analysis is not a routine screening in Vietnamese hospitals. We plan to build National Center for genetic analysis of inherited diseases where we can receive patients or their samples for confirming diagnosis. The screening guideline for medical centers base on clinical features and routine laboratory findings is very important.

Responses to Referee 1’s comments
1. Thank you very much for your comments. In this case, we excluded AIN clinically. Typically, AIN patients present mild but recurrent infections despite severe neutropenia. AIN is generally diagnosed at 8 months old and disappears around age of 2-3 year. When applying hydrocortison loading test, ANC of AIN patients are usually increased; their bone marrow test is usually normal. In contrast, our patient is six years old. He had severe neutropenia and life-threatening infections in many times. After using solumedron, his ANC was extremilly reduced and the patient was overwhelming infections. Moreover, his bone marrow test showed reduced granulocyte cell line. Therefore, SCN was suspected. Based on our case and literatures, we would like to suggest a brief guide: patients with chronic-severe neutropenia from early infancy, recurrent life-threatening infections, negative hydrocortison loading test, and bone marrow test with a myeloid “maturation arrest” at the promyelocyte-myelocyte stage of development, should be considered to genetic analysis for confirming diagnosis of SCN. The \textit{ELANE} gene should be analyzed firstly because it is the most common gene alteration in SCN.

2. Genetic analysis is not a routine screening in all Vietnamese hospitals but several advanced medical centers can do. The cost of the analysis is expensive in Vietnam, a developing country. So, the detailed screening guideline for medical centers based on clinical features and routine laboratory findings is very important. When patients are suspected SCN, their genomic DNA will be isolated and send to genetic analysis centers. We plan to build National Center for genetic analysis of inherited diseases where we can receive patients or their samples for confirming diagnosis. We appreciate your comments.
Responses to Referee 2’s comments

1. Thank you very much for your comments. Genetic analysis is not a routine screening in all Vietnamese hospitals but several advanced medical centers can do. The cost of the analysis is expensive in Vietnam, a low-income country. So, the detailed screening guideline for medical centers based on clinical features and routine laboratory findings is very important. When patients are suspected SCN, their genomic DNA will be isolated and send to genetic analysis centers. We plan to build National Center for genetic analysis of inherited diseases where we can receive patients or their samples for confirming diagnosis. The Vietnamese population is about 90 million. As the estimated incidence of SCN is 1/200 000, it is suggested that many SCN cases in Vietnam may be misdiagnosed and miss the early treatment period. We appreciate your comments.

2. It is very difficult for us to specify AIN or SCN, which occasionally caused increased ANC of the patient. We are sorry about that.

3. Thank you very much for your comments. We think that a bone marrow aspiration test should not be done when a patient has severe infections, especially skin infection in which we would like to perform this test. The bone marrow aspiration test is not expensive and covered by health insurance system in Vietnam. The test will be done in most Vietnamese children hospitals.