Skin prick test with oral streptococcal antigen as a new diagnostic test for Behçet's Disease

Thesis

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Marwa Magdi

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List of Abbreviations

µm	micrometer
95% CI	95% Confidence Interval
AIDS	Acquired Immune Deficiency Syndrome
ANA	Anti-Nuclear Antibody
ATP	Adenosine Triphosphate
AUC	Area under the ROC Curve
BD	Behçet's Disease
C3	Complement 3
CBC	Complete Blood Count
CMV	Cytomegalovirus
CNS	Central Nervous System
CT	Computed Tomography
DNA	Deoxyribonucleic Acid
EBV	Epstein - Barr Virus
EN	Erythema Nodosum
ESR	Erythrocyte Sedimentation rate
FNR	False Negative Rate
FPR	False Positive Rate
FS	Filter-Sterilized
FSS SPT	Filtered Self-Saliva Skin Prick Test
GI	Gastrointestinal
GU	Genital Ulcers
h	hour
HCl	Hydrogen Chloride
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen

List of Abbreviations (Continued)

HSP	Heat Shock Protein
HSV	Herpes Simplex Virus
ICBD	International Criteria for Behçet's Disease
IFNα	Interferon Alpha
Ig	Immunoglobulin
IL	Interleukin
ISG	International Study Group
LR-	Negative Likelihood Ratio
LR+	Positive likelihood ratio
M/F	Male/Female
MAGIC	Mouth and Genital Ulcers with Inflamed Cartilage
mm	millimeter
MRI	Magnetic Resonance Imaging
MS	Mitis-Salivarius
n	number
NAD	No Abnormality Detected
nm	Nano Meter
NPV	Negative predictive value
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
NSS SPT	Non-Filtered Self-Saliva Skin Prick Test
OR	Odds Ratio
PBMCs	Peripheral Blood Mononuclear Cells
PFAPA	Periodic Fever, Aphthosis, Pharyngitis, and Adenitis
PPV	Positive Predictive Value

List of Abbreviations (Continued)

PT.....Pathergy Test

PTX .....Pentoxifylline

RAS .....Recurrent Aphthous Stomatitis

ROC.....Receiver-Operating Characteristic

RR .....Relative Risk

S. mitis .....Streptococcus Mitis

S. sanguis.....Streptococcus Sanguis

SE.....Standard Error

SpxB.....Pyruvate Oxidase

Th1.....T-lymphocyte helper 1

TLC.....Total Leucocytic Count

TLR .....Toll Like Receptor

TNF-α .....Tumor Necrosis Factor Alpha

USA .....United States of America

VZV.....Varicella-Zoster Virus

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ABSTRACT

Background: Behçet's disease (BD) is a rare systemic vasculitis disorder of unknown etiology characterized by recurrent attacks of oral aphthous ulcers, genital sores and ocular lesion (triple-symptoms complex). Although the actual aetiology of BD is still unclear, the pathogenesis has been generally clearer by the etiological research based on the genetic intrinsic factors and immunological reactions to the extrinsic triggering factors in environmental agents.

Aim of the Work: To determine the reliability of skin prick test using streptococcal antigen extracted from saliva of Behçet patient, for in vivo diagnosis of Behçet disease in comparison to the usual pathergy test.

Patients and Methods: The study is a cross sectional study that was carried out from July 2017 to April 2019 at inpatient and outpatient clinic.

Results: All these results showed that skin prick test using streptococcal antigen extracted from saliva of Behçet patient could be a new diagnostic test for Behçet's disease. The diagnostic accuracy of skin prick using streptococcal antigen extracted from saliva of Behçet patient in Behçet's disease is 81.7%%, with sensitivity = 63.3%, specificity = 100%, positive predicted value = 100% and negative predicted value = 73.17%.

Conclusion: Skin prick test using streptococcal antigen extracted from saliva of Behçet patient showed a good diagnostic value in Behçet's disease

Keywords: Behçet disease, skin prick test using streptococcal antigen extracted from saliva of Behçet patient, recurrent oral aphthosis, pathergy reaction.

INTRODUCTION

Behçet disease is a rare vasculitic disorder that is characterized by a triple-symptom complex of recurrent oral aphthous ulcers, genital ulcers, and uveitis ***(Alpsoy, 2016).*** Although the actual aetiology of BD is still unclear, the pathogenesis has been generally clearer by the etiological research based on the genetic intrinsic factors and immunological reactions to the extrinsic triggering factors in environmental agents ***(Altenburg et al., 2006).***

As one of the triggering factors, the oral unhygienic condition may be suspected, because periodontitis, decayed teeth and chronic tonsillitis are frequently noted in the oral cavity of BD patients ***(Mumcu et al., 2004).*** The infectious triggering factors are suspected to be many organisms including streptococci and herpes simplex viruses (HSVs) ***(Galeone et al., 2012).***

The proportion of Streptococcus sanguinis (S. sanguinis), which was previously recognized as species of the genus Streptococcus named “S. sanguis,” was significantly high in the oral bacterial flora of BD patients in comparison with those of healthy controls ***(Kaneko et al., 2008).*** Most of the patients tend to acquire hypersensitivity against streptococci in their oral bacterial flora, as much stronger cutaneous reactions were seen by

the prick with streptococcal antigen than those by "Pathergy test" ***(Kaneko et al., 2014).*** In vitro system, inflammatory cytokines, interleukin (IL)-6, and interferon (IFN)-γ were produced from peripheral blood mononuclear cells (PBMCs) of BD patients, which were stimulated by streptococcal antigen, and the serum-antibody titers against streptococci were also elevated in BD patients ***(Kaneko et al., 2016).***

The diagnosis of BD is not thought to be difficult for the clinically typical cases who are based on the diagnostic criteria by Japanese and/or International Study Group ***(Krokawa and Suzuki, 2004),*** except for the atypical cases without the main mucocutaneous symptoms including recurrent Aphthous ulceration.

Pathergy test has been thought to be helpful for making a diagnosis of BD for long time ***(Kaneko et al., 2014),*** Pathergy was regarded as pathognomonic of BD because it was absent in control groups with recurrent aphthous stomatitis and systemic lupus erythematosus. It is used to describe hyper-reactivity of the skin that occurs in response to minimal trauma. A positive skin pathergy test (SPT), characterised by erythematous induration at the site of the needle stick with a small pustule containing sterile pus at its centre, and is among the criteria required for a diagnosis of Behçet's disease ***(Varol et al., 2010).***