THE JOURNAL OF
SEXUAL MEDICINE

EJACULATORY FUNCTION

Relationship Between Amyloid Precursor Protein in Seminal Plasma and Abnormal Penile Sympathetic Skin Response in Lifelong Premature Ejaculation

Zhiwei Hong, PhD Candidate,[1,*] Yuming Feng, MD,[1,*] Hualong Ding, MD,[1,*] Xuechun Hu, PhD Candidate,[1] Jin-Chun Lu, MD, PhD,[1,2] Xie Ge, PhD,[1] Yifeng Ge, MD,[1] and Bing Yao, MD, PhD[1]

ABSTRACT

Introduction: Hyperactivity of the sympathetic nervous system can play an important role in lifelong premature ejaculation (PE). Our previous study found that amyloid precursor protein (APP) levels in seminal plasma of patients with PE were clearly increased. Amyloid-β (Aβ) is derived from APP. Excessive Aβ, especially Aβ42, can cause neuronal dysfunction.

Aim: To determine whether APP and Aβ42 are associated with an abnormal penile sympathetic skin response (PSSR).

Methods: From November 2015 to April 2016, 24 patients with lifelong PE (mean age = 29.2 ± 5.3) with self-estimated intravaginal ejaculatory latency time no longer than 2 minutes and 10 control subjects (mean age = 28.0 ± 5.5) were enrolled consecutively from andrology clinics. PSSR was measured in patients with lifelong PE. APP and Aβ42 levels in seminal plasma were determined.

Main Outcome Measures: PSSR in patients with lifelong PE and APP and Aβ42 levels in all subjects.

Results: Patients with PE presented 1.5-fold higher levels of APP ($P = .004$) than control subjects. Seminal plasma protein concentration (C) in the PE group was lower than that in the control group ($P = .007$). APP divided by C (APP/C) was 2.0-fold higher ($P < .001$) in the PE group. Aβ42 level was not different between the PE and control groups, but Aβ42 divided by C (Aβ42/C) was significantly higher in the PE group ($P < .001$). No differences in APP and APP/C were found between patients with PE in the abnormal and normal PSSR groups. The abnormal PSSR group presented significantly higher Aβ42 ($P = .007$) and Aβ42/C ($P < .001$) levels. The latency of PSSR was negatively correlated with Aβ42/C ($r = -0.436$; $P = .033$).

Conclusion: These results showed that patients with lifelong PE had higher APP and Aβ42 levels in seminal plasma. Abnormal PSSR was related to a higher Aβ42 level. Drugs that decrease Aβ could be treatment of PE.

J Sex Med 2017;14:98–105.

Key Words: Premature Ejaculation; Penile Skin Sympathetic Response; Amyloid Precursor Protein; Amyloid-β; Seminal Plasma Protein

INTRODUCTION

In 2014, the International Society for Sexual Medicine defined lifelong and acquired premature ejaculation (PE) as (i) ejaculation that always or nearly always occurs before or within approximately 1 minute of vaginal penetration from the first sexual experience (lifelong PE) or a clinically significant and bothersome decrease in latency time, often no longer than approximately 3 minutes (acquired PE); (ii) the inability to delay ejaculation at all or nearly all vaginal penetrations; and (iii) negative personal consequences such as distress, bother, frustration, and/or the avoidance of sexual intimacy.[1]

Acquired PE is most commonly due to sexual performance anxiety, psychological problems, or erectile dysfunction and is occasionally due to prostatitis, hyperthyroidism, or withdrawal or detoxification from prescribed or recreational drugs.[1] In these cases, acquired PE can often be reversed after treatment of the underlying disorder.[2,3] In addition, recent studies have suggested that neurobiological and genetic variations could contribute to

Received July 5, 2016. Accepted November 1, 2016.

[1]Center for Reproductive Medicine, Jinling Hospital, Medical School of Nanjing University, Nanjing, China;

[2]Department of Laboratory Science, Nanjing Hospital, Jiangsu Corps, The Armed Police Force, PLA, Nanjing, China

*Equivalent contribution.

http://dx.doi.org/10.1016/j.jsxm.2016.11.002

the pathophysiology of lifelong PE in some men.[4–6] Although great progress has been made in the etiology of PE, the exact mechanism of PE remains unknown.

Assalian[7] first proposed that hyperactivity of the sympathetic nervous system could be a cause of lifelong PE. Recently, it was reported that sympathetic activity is increased in men with lifelong PE after measuring 24-hour heart rate variability (HRV).[8] HRV and rhythm are largely mediated through the autonomic nervous system, and the degree of HRV depends on the influence of sympathetic and parasympathetic activity on the sinus node.[9] Thus, HRV reflects spontaneous changes in autonomic activity. Their results indicated that sympathetic overactivity might lead to lifelong PE. Another study found that patients with lifelong PE had hyperactivity of the sympathetic nervous system. The latency of the penile sympathetic skin response (PSSR) was significantly shorter and the amplitude of the PSSR was significantly larger in patients with lifelong PE compared with normally potent men.[10] Furthermore, the amplitude of PSSR in patients with lifelong PE was decreased and the latency of PSSR was prolonged after 8-week sertraline treatment.[11]

Our previous study showed that patients with PE had higher amyloid precursor protein (APP) levels in seminal plasma compared with the control group.[12] APP is a ubiquitously expressed membrane protein with a domain structure that resembles a typical membrane receptor protein.[13] Amyloid-β (Aβ) is derived from the proteolytic cleavage of APP.[14] It has been reported that Aβ is neurotoxic to mature neurons at higher concentrations and causes dendritic and axonal retraction followed by neuronal death.[15] In transgenic mice overexpressing APP, Chapman et al[16] reported severe impairment in long-term potentiation in the dentate gyrus regions of the hippocampus, indicating Aβ could affect the electrical activity of neurons. Aβ could damage neurons and increase their vulnerability to excitotoxicity and the mechanism might involve the generation of oxyradicals and impairment of membrane transport systems.[17] Membrane transport systems are important for neurons to maintain voltage gradients across their membranes and the damage of membrane transport systems can result in neuronal dysfunction. These results indicate that excessive Aβ can cause neuronal dysfunction. Several lines of evidence have shown that Aβ42 might be the more toxic species.[18–21] Therefore, we propose that APP and its proteolytic peptide Aβ42 might be associated with neural dysfunction in patients with PE. The aim of this study was to determine whether APP and Aβ42 were associated with abnormal PSSR.

METHODS

Subjects

From November 2015 to April 2016, we recruited 24 patients with lifelong PE who sought treatment for PE in andrology clinics. Another 10 healthy volunteers without complaints of PE or other sexual dysfunction from the andrology clinics with healthy physical examination findings were enrolled as a control group. The study was performed in accordance with the Declaration of Helsinki and was approved by the ethics committee of Jinling Hospital (Nanjing, China).

Lifelong PE was defined as ejaculation that always or nearly always occurred within approximately 1 minute of vaginal penetration from the first sexual experience. Because Waldinger[22] reported that most men with lifelong PE ejaculated within 1 minute but that approximately 10% of an entire random cohort ejaculated within 2 minutes, patients who ejaculated always or nearly always before approximately 2 minutes of vaginal penetration from the first sexual experience were included as having lifelong PE. In addition, patients with lifelong PE had to be in a heterosexual, stable, and monogamous sexual relationship with the same female partner for at least 6 months. The exclusion criteria were (i) secondary PE; (ii) abnormal routine physical and neurologic examination results; (iii) erectile dysfunction; (iv) psychological problems or somatic diseases, including genitourinary tract infection and hyperthyroidism; (v) any condition that could affect sympathetic activity, such as cardiac arrhythmia, hypertension, diabetes, or taking any drug that could affect sympathetic activity; and (vi) any drugs that affect sexual function or psychological status (eg, selective serotonin reuptake inhibitors and phosphodiesterase type 5 inhibitors).

Demographic Characteristics and Questionnaires

All participants provided written informed consent before their participation. All patients underwent a complete andrology and physical examination. The participants also were asked to complete questionnaires on demographics, self-estimated intravaginal ejaculatory latency time, the Premature Ejaculation Diagnostic Tool (PEDT), and the International Index of Erectile Function−15.

PSSR Recording

Details of the PSSR recording method were reported in a previous study.[10] Briefly, recording ring electrodes were placed around the proximal (cathode) and distal (anode) regions of the penile shaft at a distance of 2 cm. The ground electrode was placed on the right wrist. Skin impedance was decreased below 5 kΩ with conductive gel. Electric stimulation was applied through superficial electrodes over the right median nerve. The PSSR waveforms were obtained using an electrical shock consisting of a single square wave pulse of 1-ms duration and 70-mA intensity. Three stimuli were administered at irregular randomized intervals longer than 30 seconds. PSSR latencies were measured from the origin of the trace to the first deflection of the trace from baseline, and the amplitudes were assessed by peak-to-peak analysis (from the first peak to the following opposite trough). The average amplitude and mean latency were used for analysis in each subject.