Volume 2 • Issue 1 • 2020

Short Communication

Journal of Gynaecology and Paediatric Care

PMLCP is a Clinical test Related to Cognition, its Research Ideas

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Received: June 16, 2020; **Published:** June 26, 2020

Focusing on the exploration of the etiology and prevention of Alzheimer's disease, "Although there have been more than 100 relevant clinical trials conducted worldwide, unfortunately, no one has developed therapies and drugs that can terminate the AD process." The theme of the new World Alzheimer's Day is "Remember 3 seconds" to remind us that there will be an Alzheimer's disease patient every 3 seconds in the world, which requires people to take active action. So, what is the biggest difference between the newly launched "Complete Menopause Leading Cognition Project" (PMLCP) and these implemented projects? Why would the focus of intervention be re-selected in the menopausal population?

In the past three years, in the published trial project, "a clinical trial has recently brought hope: paying attention to lifestyle habits such as diet and exercise may prevent dementia." In the study, "when the subjects follow relevant health care When taking measures, their cognitive activities such as memory and thinking sensitivity have made significant progress. Although the "Finnish Intervention Study on Prevention of Cognitive Impairment and Cognitive Impairment in the Elderly" (FINGER) started in 2012, its findings are "sufficient to provide people with dementia prevention through multiple means such as diet, exercise and social integration. References ". However, it is worth noting that the project host Mia Kivyperto (Professor of Clinical Geriatric Epidemiology, Karolinska Institutet, Sweden), stated in her "Life Therapy for Dementia" article: "Another analysis believes that the number of subjects with cognitive deterioration can be used as an indicator," which indicates that there are still some cases of cognitive deterioration while conducting the FINGER study to prevent dementia. That is to say, only through the two most important protective factors such as sports and social and cognitive activities, FINGER cannot completely prevent cognitive deterioration. Therefore, we still need to face and understand what are the risk factors, and what kind of harmful environment can be exposed (FINGER), but also can continue to worsen cognition? As Professor Gu Fan and Professor of the School of Life Sciences at Fudan University in Shanghai said in the article "Global Brain Project" for Scientific American in 2017: "Even though the tasks of diagnosing, treating and preventing Alzheimer's sound sound clear, but so far, The scientific community has no theoretical framework for brain function. "

After sorting out the research of the past century, Dr. Alzheimer's clinical experience and anatomist's thinking or specialty (using a scalpel and a microscope) have been studied in depth, which has made us obtain an extremely rare symptom. The association with the anatomy and the corresponding case No. 0 were established. Although the existing clinical symptom records and anatomical records only contain three sentences, the relevant symptom parts: 1. Her memory has seriously deteriorated, 2. It is very difficult to communicate with others, 3. She suspects her husband's infidelity for no reason. Regarding the anatomy, under the microscope: 1. The cerebral cortex is severely atrophied, 2. There are a large number of necrotic nerve cells in the brain, 3. There are many abnormal protein deposits in the brain.

The early exploration and prevention are mainly considered at the macro level, aiming at the occurrence of symptoms. The biological and physical changes in the brain are beyond the consideration of scientists. For these symptoms, many people have realized that it may be associated with menopausal physiological changes and menopausal syndrome. Twenty-six years after the definition of AD, Geist and Spielman first used estrogen preparations to prevent and treat menopausal syndrome in 1932; after 31 years of exploration, in 1963 Rober Wilson first realized that supplementing estrogen to postmenopausal women can not only treat menopause The various symptoms can also delay and prevent the occurrence of diseases related to menopause. This method is called estrogen replacement therapy (ERT). In the meantime, in order to cope with the occurrence of endometrial cancer, progestogens were also introduced, and are collectively called hormone replacement therapy (HRT). 55 years after the exploration and application of estrogen, in 1987, the academic circles stated in the textbook "Obstetrics and Gynecology" that "menopausal syndrome is mainly related to the decline of sex hormones." In fact, which sex hormones decline? What is the role of different sex hormones? Why does the decline cause menopausal syndrome? It has not been clarified. Nevertheless, in the same year, 81 years after the definition of AD, scientists also introduced many new technologies from basic disciplines, such as magnetic resonance imaging, positron emission tomography (PET), etc., they turned their attention to brain anatomy Recorded and began to "establish the hypothesis of amyloid beta and Tau protein" at the molecular level. "Most scientists seem to think that these two proteins accumulate in the brain in large amounts to cause AD to occur." It can be found that the exploration of the prevention and treatment of AD is generally carried out according to the two paths of clinical symptom records and anatomical records.

After 68 years of exploration and application of estrogen, in 2000, the academic circle once again stated through the textbook "Obstetrics and Gynecology" that "In recent years, studies have found that estrogen deficiency may have a potential risk of Alzheimer dementia, manifested as dementia, memory loss and aphasia Recognition, directional calculation, judgmental disorder, and changes in personality, behavior, and mood. "However, some subsequent well-known clinical studies such as:" Women's Health Leading Memory Research "(WHIMS) more than 4,000 women participated, taking estrogen for 4 and a half years, but The number of patients with Alzheimer's disease has tripled, and it has also increased the risk of breast cancer and stroke. In view of the significant health risks of estrogen therapy, "WHI research suggests that estrogen replacement therapy should not be used as a routine treatment for postmenopausal women." It is a pity that from 1932 to 75 years in 2007, only according to the idea of what is missing and what to make up, expecting estrogen to solve all menopausal problems including AD attempts, seems to have entered a dead end.

In another exploration path, after the protein hypothesis was established, despite the "overexpression" of what caused it, it has not been clarified. However, based on these two protein hypotheses, related targets have been developed. Sixteen years later, the first (and only) therapeutic drug "Memantine" was launched in 2003. Subsequently, "a dozen drug candidates failed in succession, the most recent failure was in April 2019." The protein hypothesis has been running for 32 years from 1987 to 2019. People start with anatomical records and try to "suppress" or "clear" according to the idea of "what is redundant, what is eliminated". After huge investment and various efforts, it seems to have almost become a bubble.

Therefore, what is the nature of menopausal syndrome? Which sex hormones decline? What is the role of different sex hormones? What is the corresponding operating mechanism? What are the risk factors? What causes "overexpression"? High-risk groups? What is the harmful environment and the exposure of the harmful environment? These deep questions still need people's attention, exploration and clarification.

In recent years, we (the two authors of this article, Cha Jianzhong and Li Songlin) have published a series of related articles (including "Menopausal Sexual Characteristics", "Exploring Hormone Imbalance", "Sex Stress" A Hidden Source of Stress, etc.), explored and elaborated on these questions, and tried to try to integrate some harmful factors or possible pathogenic mechanisms linearly, and figure out the approximate sequence and causality.

From the menopausal sex that appears to be "thinking" but "can't" the difficult situation of sex, it can be found that there is a material basis for human sexual instinct. Over the past century, a lot of observations have shown that androgen (T) is positively related to sexual desire, which is a sufficient condition for female sex. "Estrogen (E2) can stimulate the secretory function of secretory cells and play an important role in producing vaginal lubrication." It is a necessary condition for female sex. T and E2 determine "think and energy" respectively, and become the material basis of female sexual instinct.

Usually in the sexual experience of "reproductive sex", sex is only confirmed "think of it". However, from the dimension of species reproductive competition, it is found that animal reflex ovulation (as long as mating can ovulate) has obvious reproductive advantages over human ovulation. As a kind of compensation, humans match the ovarian secretion of T and E2 autonomously and periodically, and correspond to the peaks respectively during ovulation. T will help the occurrence of "active sex" and facilitate the meeting of "sperm and egg". Reproductive tips ", and E2 will provide support for lubrication (entrance), keratosis of the vaginal mucosa (tolerance to exercise ejaculation), thus forming a reproductive compensation mechanism.

When menopause comes, this mechanism will not be compensated for infertility due to apoptosis in reproductive function. "E2 does not gradually decrease during the entire menopausal transition period, but only drops rapidly when the follicles stop growing and then shuts down after menopause." After the compensation mechanism was withdrawn, "hormone T decreased by 29% and 71% left, while E2 fell by 85% and only 15% left," thus losing the original autonomous and rapid lubricating ability in menopausal sex. "50% of women have pain after sexual intercourse and difficulty in sexual intercourse" after entering menopause.

Difficulty in sex means that the physical and social needs (harmony of the family) cannot be met well. Not only will it cause major problems for the relationship between the sexes, but it will also involve minor and frequent troubles in daily life, making stress everywhere. As hormone levels increase and decrease, sexual stress caused by sexual demands will continue to appear periodically and periodically. Under the influence of social restraint system (marriage, secular, etc.), the sexual needs of spouses (partners) are still only obtained from menopausal women. Due to the lack of sex, this group of people often suffers from the negative feelings of weakness and inferiority in.

Physiological changes in menopause, especially for more than half a century, from theoretical exploration to practical verification (including estrogen deficiency theory, as well as ERT and HRT). Due to the fact that the theoretical failure and the defects of the method, this brings entanglement and anxiety to the menopausal people. Because "disease medicine and sex medicine have differences in the judgment of" disease ", for a long time," many doctors believe that sexual problems are caused by psychological factors "and even think that" FSD is an artificial disease. "Until today, on the global scale, sex studies and the gynecology community has not been able to properly solve these practical problems faced by menopausal women." Long-term neglect" has become a relatively common situation.

In addition, the "aging theory" has always become the most natural and obvious cause of menopausal sexual difficulties. "The changes in menopause actually include two aspects: one is the impact of ovarian function decline and the level of estrogen in the body; the other there are also changes in the aging of the organism, and the two are often intertwined. "In fact, after the withdrawal of compensation, the body provides lubricating support for climacteric and non-reproductive sex by means of" reflective secretion" Necessarily related.

For theoretical failures, method flaws, "artificial diseases" and "aging" etc., the individual is unable to cope. The syndrome happens during this change or in an attempt to prevent it. According to psychobiology, "the process of adaptability and coping response when an individual faces or perceives environmental changes as a threat or challenge to the body is stress." Therefore, menopause syndrome is essentially a Individuals believe that they have not responded to possible negative stress responses. And "with negative emotions and individuals believe that there is no possible response to coping with stress, causing anxiety, cognitive decline, mood swings, and confusion." It is also the view of psychobiology.

In 2012, Yale University School of Medicine published a related research result, "Stress destroys self-control", revealing several important relationships between stress and the brain: "The prefrontal lobe plays an unexpected role and can coordinate as a control center when there is no stress: Advanced cognitive functions such as judgment, decision-making ability, and recall ability, "under long-term pressure," the neuronal dendrites in the prefrontal cortex have shrunk and can also cause the area responsible for logical reasoning to start to shrink. " When they disappear, the dendrites of prefrontal neurons will regenerate. If the pressure is too high, this regenerative ability will disappear. "Research also shows that" tremendous, uncontrollable pressure can cause neurons between when the connection is interrupted, the function of the prefrontal cortex will be turned off. "A. Arnsten, a professor of neurobiology, and others in this joint study further clarified the effect of stress on the brain from the molecular level.

A public study in June 2017 showed that the "community (large sample) cohort study" that began in Shanghai, China, was designed to "help older people stay away from AD as much as possible." However, "even if they observe, they do n't know at what age should the starting point of observation be set? "Project leader Pei Gang, academician of the Chinese Academy of Sciences, Shanghai Institute of Biochemistry and Cell Biology Point. "And" Almost 300 of the 700 people who were examined were found to have cognitive decline. "

China "The average age of menopause in urban women is 49.5 years, and the transition period of menopause lasts about 4 years. One-third of women will be asymptomatic, and two-thirds of women will have premenopausal syndrome. Nodes that have undergone a four-year transition period are just proof that in menopause, in a harmful environment that can produce negative stress, they will face the risk of cognitive damage. It can be inferred that under natural conditions, about 42% (300/700) of people who experience menopause have cognitive decline, while about 64% of people who have menopausal syndrome have cognitive decline.

"Because menopausal people need to deal with these physiological, psychological and sociological problems in a concentrated and intensive manner, they will usually be under limited pressure for a long time and will face the risk of excessive or even great pressure." One group will become a high-risk group with a risk of cognitive impairment.

So far, the "pressure theory" of menopause has initially constructed a theoretical framework related to cognitive impairment. The core idea is that individuals believe that failure to cope with possible negative stress is a risk factor for cognitive impairment, and the environment that can produce such negative stress is a harmful environment for cognitive problems.

In February 2019, we (two authors of this article, Cha Jianzhong and Li Songlin) used this framework for the first time to interpret Case No. 0 of AD and put forward new views on "overexpression". "After repeatedly experiencing that the individual believes that there is no possible negative stress, while continuously weakening the cognitive ability of the brain, atrophy and necrotic nerve cells are continuously deposited, and this leaves anatomical evidence for these processes."

As Frank Wilczek, (2004 Nobel Prize winner) put it, "We need to clarify and repeatedly verify our hypothesis, and revise it if necessary, so that scientific research remains honest and credible."

Based on this framework, the clinical study of the "Perfect Menopause Leading Cognition Project" (PMLCP) is intended to recruit menopausal subjects (including their spouses or partners) as a treatment group.) Cohort study"is the control group. The treatment group will help the subjects "start (adapt) the reflex lubrication system and maintain (restore) the regular sex life" through sex education and the prevention and treatment of FSD to achieve a full menopause. By jointly creating an ecosystem suitable for the brain, the risk of cognitive damage caused by long-term exposure to harmful environments due to menopause problems is reduced or eliminated. It is hoped that the results of the treatment group and the control group will be compared to verify that the individual believes that there is no causal relationship between possible negative stress and cognitive impairment.

In January 2020, Claudia Wallis, former editor-in-chief of Scientific American Spirit, wrote: "Current support for the amyloid hypothesis has blocked the way to explore other directions, it is time to bypass amyloid this target."

PMLCP, like all efforts, aims to find a new direction and get rid of the predicament.

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