

Exploring the Causes of Alzheimer's Disease - Interpreting Auguste

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Auguste, an ordinary German old woman in the early 20th century,

It is also Ales. The owner of the famous case first reported by Dr. Alzheimer.

After 112 years, although there are still many gaps between the clinical data of this case including clinical symptoms and anatomical records.

However, we can reconstruct her evolutionary history with the help of theoretical frameworks constructed in recent years.

Explore the causes of August's symptoms and prevent more Auguste reproduction.

This is a famous story that is getting more and more attention. "At a scientific conference in November 1906, there was a German doctor, Alez Alzheimer, who reported a special case. In 1901, the old woman was brought home by a family member. At the time she had severely lost her memory, it was very difficult to communicate with others, and she doubted her husband's infidelity for no reason. In the following years, her condition deteriorated sharply. In the spring of 1906, she was suffering from pneumonia and acne. Dr. Alzheimer has never seen such a strange case before, and he has done an autopsy on the old woman after obtaining the consent of the patient's family. He found that the old woman's brain is especially The cerebral cortex is severely atrophied (we know that the cerebral cortex is our memory, language, and thinking) and under the microscope, the doctor sees that there are a lot of necrotic nerve cells in her brain, and there are many abnormalities. The deposition of protein. Later, in order to commemorate the German doctor, the disease was called Alzheimer's disease, which is what we said. Farmer's disease".

Obviously, Alzheimer's disease has been associated with women, menopausal physiological changes, gynecology, human sex, neuroscience, and sociology since its definition. So what is the cause of this strange symptom? For more than a century, people have tried to find some answers by discussing the issues related to women and menopause. After Alzheimer's disease, 26 years later, in 1932 Geist and Spielman first used estrogen to prevent menopausal syndrome. 57 years later, in 1963, Rober Wilson first recognized the supplementation of estrogen to postmenopausal women, not only for treatment. Various symptoms caused by menopause can also delay and prevent the occurrence of diseases related to menopause. This method is called estrogen replacement therapy (ERT). However, in order to cope with the occurrence of endometrial cancer, progesterone is introduced, and is collectively referred to as hormone replacement therapy (HRT). 81 years later, in 1987, the academic community officially stated in its textbook "Gynecology and Obstetrics" that the menopausal syndrome "is mainly related to the decline of sex hormones". 94 years later, in 2000, the academic community officially stated in its textbook "Gynecology and Obstetrics" that "recent studies have found that estrogen deficiency may be potentially dangerous for Alzheimer's dementia, manifested as senile dementia, memory loss, aphasia, Directional calculations determine obstacles, and personality behavior changes". However, some of the well-known clinical studies such as "WHIMS" involved more than 4,000 women, taking estrogen for 4 and a half years, but the number of patients with Alzheimer's disease has tripled. It also increases the risk of breast cancer and stroke risk. Given some of the major health risks of estrogen therapy, "WHI's research suggests not using estrogen replacement therapy as a routine

treatment for postmenopausal women". Regrettably, from the years of 1932 to the present, according to the "lack of what, what to add" thinking, expecting estrogen to solve all menopausal problems including AD attempts, seems to have entered a dead end.

But in any case, when women experience physiological changes, the results of the decline in sex hormones are unquestionable. In exploring this strange case, the anatomical structural abnormalities she left are also not to be ignored. A major challenge in the academic world is to find out the causes and mechanisms of Alzheimer's disease. 81 years later, since 1987, at the molecular level, "the hypothesis of beta amyloid and Tau protein has been established in the academic world". "Most scientists seem to think that these two proteins aggregate in the brain and cause Alzheimer. The disease occurs". Although "overexpression" or "mass release" or "metabolism" has not been elucidated so far, the industry has developed relevant targets based on the theoretical basis of these two protein hypotheses for drug development. In view of the results of a large amount of aggregation or over-expression, according to the idea of "what is unnecessary, what to remove", and for the two targets, the development design of inhibitors or scavengers has appeared, and even the most powerful one is inhibited. Intervention method. "At present, most of the research and development of major companies around the world have developed pathways around these two theoretical foundations, but drug development for amyloid targets is the hardest hit by R&D failure". Unfortunately, "Mei Jingang" was awarded in 2003. In the past fifteen years, the real new drugs have not appeared again, and the R&D failure rate is almost 100%. For 40 years, people have started from anatomy, trying to find inspiration, and trying to "suppress" or "clear" according to the idea of "what is unnecessary, what to get rid of". After huge investment and various efforts, it seems Almost has become a bubble.

"The number of Alzheimer's patients increased by 66% from 2000 to 2008". After another 10 years, it is even more difficult to find that Alzheimer's disease has become "human through". The latest and greatest challenges to the longevity and health roads". In September this year, the International Alzheimer's Association published the annual report on Alzheimer's disease in the world of 2018 on the official website. "This year's theme is '3 seconds', which reminds us to add one every 3 seconds. Dementia patients. The report provides the latest disease data: there are currently 50 million dementia patients worldwide; in 2018 alone, there are an estimated 10 million new dementia patients.

As an Alzheimer's disease drug research and development "Leading Brother" Lilly, since 1988, "to date, the investment has been close to 4 billion US dollars". In an exclusive interview with the 21st Century Business Herald, Wu Shenghu, the medical director of China's central nervous system in Lilly, pointed out: "Because there is no longer a breakthrough in the theoretical foundation, there is no new theory, which is one of the reasons why the clinical success rate is too low".

In fact, there is no lack of hypothesis in exploring Alzheimer's disease (including the insights of two Nobel laureates). Perhaps we can learn from Stanley Prusina's predictions about how prion is formed, will be helpful to understand Alzheimer's disease" and Edward Moser found in "If we have a deeper understanding of grid cells and navigation systems, we can early intervention in Alzheimer's disease" Inspiration and look forward to a breakthrough. Alternatively, we can pin all our hopes on the National Alzheimer's Project Act issued in the United States in early 2012, when the US government announced "the eradication of Alzheimer's disease in 2025". The achievement of this goal has relied on the new method of "detecting the abnormal protein accumulation characteristic of Alzheimer's disease 10 to 15 years before the first onset of the disease" and "an anticancer drug can be obtained from the mouse brain". It eliminates the toxic beta amyloid produced during the onset of Alzheimer's disease. However, it seems that this road will not work.

There is another way to go back to the origin, find the prototype of AD, and use the relevant theoretical research in recent years to establish a theoretical framework for a more comprehensive and comprehensive interpretation of Auguste. By analyzing August's clinical symptoms, anatomical records, and reconstructing her historical and anatomical features, this is the approach we will describe in this article.

The earliest AD prototype

Although there are two different versions of the description of the master's situation when describing the famous case story of Dr. Alzheimer (a relatively complete picture with a photo, but no name, and another incomplete name is Auguste). In order to better understand Alzheimer's disease, we chose this full version and the name Auguste as the earliest prototype of Alzheimer's disease.

At the end of the 19th century, Auguste in the early 20th century is an era in which gynecology and human sinology need to be further developed, and it is still difficult to fully and effectively serve the clinic. At the same time, it is also in a "male" social environment. What's more is that it creates a feeling of inferiority for women. At the same time, it also highlights the concerns about women's sexual and reproductive abilities.

Auguste experienced the entire process of AD formation, and Dr. Alzheimer made a valuable clinical and anatomical record. But after 112 years, when we want to interpret Auguste, there are only three sentences to see her clinical symptom record: 1. Her memory has been seriously degraded, 2. It is very difficult to communicate with others. 3. No doubt about her husband's infidelity.

However, evidence from the evolution of the brain has been left from Auguste's anatomical record. Although this record is only three sentences (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.

For this sad photo, it is still widely circulated today that "low educated person" is a susceptible group of Alzheimer's disease. Does this hypothesis not know whether it is related to the understanding of photos?

In recent years, we (the two authors of this article, Zha Jianzhong Li Yulin, 2013) have published "Invasive (Sexual Intercourse) Pain Control Research" in the "World Health Conference" and "European Gynecology" magazine sponsored by (WAS). Four articles, such as "menopausal sexual characteristics" and "a hidden stressor of sexual stress" and "exploration of hormones imbalance", initially formed a theoretical framework for AD, providing conditions for the interpretation of Auguste.

Why do you have to interpret Auguste? Why should we pursue these original memories? In the development process of AD, in addition to being the first AD prototype, she is still an extremely rare case between the symptoms and anatomical records. Because human form will continue to evolve with the same plasticity, history will repeat itself.

Really "no reason"?

From the photos and symptoms of Auguste, it can be judged that this is a problem experienced in menopause or menopause. Auguste's complaints are usually based on the lack of or total lack of sex between husband and wife. It is also a common female sexual dysfunction (FSD) problem in menopause. Due to the hidden nature of sexual problems, they are often considered by outsiders as "no reason". In fact, for a long time, people (including academics) have always lacked attention and research on the problem of sexual difficulties (FSD) caused by menopause. In the past 30 years, the (FSD) issue has become one of the important issues in the study of the world of academics. However, only 15 years ago, in early 2003, BMJ published an article saying that "FSD is an artificial disease". Due to the influence of BMJ, this view has had a total negative impact on FSD related research (including basic, pharmaceutical, and clinical). In the following 10 years, there was no targeted response and voice from the global academic community. Only in 2013, WAS hosted the 21st World Health Conference, and selected a speech abstract, "Invasive (Sexual Intercourse) Pain Control Research", which is a discussion of "when it is difficult to make love, our body happens". "What" research is aimed at women who are disappointed, confused, and even suffering, as well as scientists and doctors who have long been misunderstood but are still trying to explore. The study included: discussion of etiology, discussion of pathology, and introduction of "medical ethics" thinking, introducing "evidence-based medicine" thinking. Studies have shown that: "Traditional medicine (disease medicine) and sexual medicine have differences in the judgment of 'disease', the two are based on 'survival' and 'quality of life'; the entry pain cannot be pleasant and does not affect survival, so Faced with traditional medicine, this is the root cause of a large number of patients seeking no medical treatment". There are indeed physiological factors in the pathology of FSD. "The strong pain can cause nerve hypersensitivity; the negative emotion caused by neurotransmitters can lead to the inhibition of the endocrine system; and

the high stretch ability of the vaginal mucosa needs to be repaired in a highly sensitive state etc. Therefore, FSD is not a disease that has been created, FSD does exist, and it is necessary to strengthen the corresponding clinical therapeutic research.

In fact, sex between husband and wife is “a physical and mental movement that requires synergy, interaction, participation and sharing”. FSD can cause sexual intercourse difficulties or failures, and long-term “sexlessness” can make both partners feel uncomfortable. Because “whether ‘pain’ is linked to whether it can ‘participate’; whether ‘true pain’ is linked to ‘emotional problem’, so FSD is no longer an individual symptom”. Because of this pain, it affects others”. “Pleasure”, bringing “uncomfortable” to others, and even more extensive. Therefore, sexual intercourse pain (FSD) becomes a related symptom. Regrettably, because the scientific community and the medical community know too little about this, and in accordance with the traditional medical thinking of disease in the investigation, they often get the conclusion that “no abnormality” is reached, which leads to “patients with painful participation - repeated deepening - Long-term unhealed, even fear of the consequences of not being able to”. Especially the sexual “sexual obligation” of marital sex, the requirement of loyalty, further caused that not making love is an emotional problem, doing a passion problem, no interaction or no passion The dilemma makes the patient in a state of extreme grievance, depression and desperation. FSD can even cause long-term asexuality (such as months, years, or even more than ten years). Therefore, this symptom often leads to “unknown fire” between husband and wife, leading to cold war, outbreak confrontation, and even incidents such as affair and divorce, causing various personality crises, which directly endangers marriage and family stability.

Therefore, the symptom of sexual intercourse pain (FSD), after being superimposed and superimposed by sociology, often produces pain beyond the pain itself. Confusion, depression, fear, tolerance, grievances, and helplessness are the conditions of patients including Auguste.

Reproductive compensation mechanism

One inference is that Auguste experienced a menopause FSD and would be a terrible situation. Is it a case or a special case? Still a high probability event? If so, why is there a menopause FSD problem?

In 2015, at the 22nd World Health Conference sponsored by WAS, a video of the conference, Dimensional Sexuality, was selected. This is a cross between human sex and gynecology. Subject research, I hope to understand how the menopause affects sex? The study divides women's life's sexual love into three different stages: reproductive stage, menopause, and non-reproductive stage, and considers the dimension of species reproductive competition. It is found that: “Animal reflex ovulation (as long as mating can ovulate), than humans The cycle of ovulation has obvious reproductive advantages. As a kind of compensation, humans use ovarian autonomic and periodic secretory hormones T (androgen) to match E2 (estrogen), and T is positively correlated with libido, which corresponds to ovulation. Peaks and peaks contribute to the occurrence of “active love”, which facilitates the “sperm egg” encounter, thus having the function of “reproductive cues”. In particular, E2 is growing and correspondingly peaking, providing sexual activity for this period. Support including lubrication (entry), vaginal mucosal keratosis (tolerance to sports ejaculation). Obviously, from the reproductive tips, to lubrication, keratinization, this series of subtle care is enough to show that this is a mechanism, one The mechanism of reproductive compensation”. Because of the role of reproductive compensation mechanism, hormone T and E2 will be normal under normal conditions for more than 30 years before women enter menopause. Remains unchanged, ensuring in this period can be reproductive, sexual able to “want to be able to”. However, “due to the onset of menopause, the reproductive function of apoptosis, the reproductive compensation mechanism will not be compensated for non-reproductive, more specifically the non-asymptotic withdrawal of the compensation mechanism”. Usually “the entire menopausal transition period E2 It does not gradually decline, but only when the follicle stops growing and developing, it drops rapidly, and after the menopause, it closes the secretion”. And this change often occurs quietly, and the sudden emergence of the cliff-type secretion stop will

directly cause the vaginal dryness, and It is easy to cause pain in sexual intercourse, which causes serious discomfort in both sex partners, causing a crisis of sexual self-confidence. Therefore, the problem of menopause FSD has become a common and frequent symptom.

Harmful environment and exposure

In 2017, a member of the Chinese Academy of Sciences, Shanghai Institute of Biochemistry and Cell Biology, researcher at the Institute of Biochemistry and Cell Biology, published an ongoing "Community (Large Sample) Cohort Study" in Scientific American magazine to explore Alzheimer Information on the cause of the disease. Handan Steel advanced the observation point to 55 years old, "this is the approximate time point at which mild cognitive impairment begins to appear", noting that "the abnormalities in depression and hormone levels can also lead to signs of mild cognitive impairment. "And nearly 300 of the more than 700 people who were examined were found to have cognitive decline".

Obviously, if you don't get proper treatment, it will be very likely that a harmful environment will occur during menopause or menopause. It can be speculated that when August has experienced menopause and female sexual dysfunction (FSD), not only will it be bad. The situation will increase the feeling of inferiority. So by the beginning of menopause, Auguste has been in a harmful environment.

According to the academic circles, the average age of menopause in urban women in China is 49.5 years old, the average age of menopause in rural women is 47.5 years, and the transition period of menopause lasts about 4 years. One third of women will be asymptomatic, and two thirds of women will be surrounded. Menopausal syndrome". It can be inferred that the cognitive decline observed by Handan Iron and Steel, from the beginning of menopause to the observation point of 55 years old, will last about seven years. Approximately 42% (300/700) of the menopausal population experienced cognitive decline, while approximately 64% of the menopausal syndrome population experienced cognitive decline. Therefore, long-term exposure to harmful environments will lead to cognitive problems.

Obviously, if the time to record the symptoms of Auguste 1901 is taken as an observation point, there should be at least 7 years (from menopause to observation point) from about 1894 to 1901. It can be considered that due to August Long-term exposure to harmful environments leads to severe memory loss and difficult to communicate with others.

According to the menopausal transition period (menopause), it will last for about 4 years. Does the harmful environment still exist after 4 years? In 2017, we (the two authors of this article, Zha Jianzhong Li Yulin), in a study on "exploring hormone imbalances", "If we combine the hormone levels of the fertile T and E2 into 100%, then, after the withdrawal mechanism, the hormone T decreased by 29%, leaving 71%. The hormone E2 actually fell by 85%, leaving only 15%. The low level of E2 is no longer enough. In order to support the formation of effective stimulation of secretory cells, and the secretion, so that lost the original spontaneous, spontaneous, automatic and rapid lubrication in menopause sex. The changed results (new hormone levels) will also It has continued for another 30 years, until the entire non-reproductive period". It can be seen that if Auguste cannot effectively solve the problems related to menopause with the help of social support systems (medical, sex education, etc.), if the relationship between the sexes cannot be achieved Balance, harmful environment will exist for a long time.

In recent years, Professor Roberta Diaz Brinton of the University of Southern California and others have proposed a hypothesis in a study, "The special physiology of women causes their brains to change, which is easy to produce Alzheimer's disease. For example, Symptoms before menopause and menopause change their brains". If this guess is correct, how does this change evolve?

Overexpression, or necrotic deposition?

"Most scientists seem to recognize that two proteins accumulate in the brain in large numbers, leading to Alzheimer's disease". And Gary Steinstein, author of the 2012 article "Destroy Alzheimer's Disease in 2025", believes that This accumulation "is the overexpression of this specific protein". How does menopause change the brain of August? Is the deposition of many abnormal proteins in the brain of Auguste "over-expressed?"

Other scholars also published a seemingly unrelated research result in 2012, "Prevention of Self-control by Pressure", but it is worthy of attention. Amy Arnsten, a professor of neurobiology at Yale University School of Medicine, and others in this joint study reveal several important relationships between stress and the brain: "The prefrontal lobes play an unexpected role, no stress At the time, it can be used as a control center to coordinate: advanced cognitive functions such as judgment, decision-making ability, and recall ability", and is "sensitive to even temporary stress and worry about even temporary stress, even for mild stress". Under stress, "the dendrites in the prefrontal cortex are atrophied, and can also cause the area responsible for logical reasoning to begin to shrink". However, "once the pressure disappears", the dendrites of the prefrontal neurons regenerate. If the pressure is too high, this regenerative power will disappear. "The study also showed that "the huge, uncontrollable pressure causes disruption of the connections between neurons in the prefrontal cortex and the function of the prefrontal cortex is turned off". At the same time, the brain transfers control of thought and emotion from the prefrontal cortex to a more primitive area".

In 2017, we (the two authors of this article, Zha Jianzhong Li Yulin) draw on these research findings on stress and brain neural mechanisms, from the perspectives of human ethics, gynecology, psychobiology, brain evolution, and mathematical analysis. The concept and method of the subject, a multidisciplinary study, "Sexual Stress Sources of Sexual Stress", to explore whether the relationship between menopausal changes and menopausal syndrome is associated with Alzheimer's disease. Studies have shown that: "The common suspicious, anxiety, and depression of menopausal syndrome is a negative stress response. Sexual stress is a hidden source of stress in the response; the reproductive compensation mechanism is not asymptotically withdrawn. It is the cause of prevalence of sexual stress in menopausal women; because FSD is associated with symptoms, sexual stress may lead to repeated and persistent stress". The study concluded that "sexual stress is a category of stress that is prone to persistence, Potentially uncontrollable features. Significantly associated with menopausal syndrome, is a hidden source of stress and associated with Alzheimer's disease through negative stress".

"The suspicion of husband's infidelity for no reason" is both a stress response of Auguste and also shows that she is already under pressure. According to the "Social Re-Adaptation Assessment Form" (SRRS) of Thomas Holmes and Richard Rae, "divorce" is the top-ranked and most stressful life event based on the severity of the stressors. First, "infidelity" has a direct connection with "divorce". From the photos, Auguste may also have low education and economic dependence. It can be seen that she has been under a lot of pressure and is very likely to have a huge and uncontrollable situation. "When the pressure is too high, the damage to the prefrontal neurons will be irreversible. If such pressures occur repeatedly, because they are irreparable and accumulating, they will constantly weaken the cognitive ability of the brain and become a hidden attack. The process of changing brain function".

That is to say, Auguste has experienced varying degrees of pressure on the timeline of Handan Iron and Steel (the seven years from the menopause to the observation point) and the timeline of August (during five years of deterioration). While constantly weakening the cognitive capacity of the brain, atrophic, necrotic nerve cells are also constantly depositing, leaving anatomical evidence for these processes. It can be seen that the hypothesis of "stress" is more rigorous than "overexpression".

Since the occurrence of Alzheimer's disease, people have gradually realized that estrogen reduction has been a way of withdrawing from the mechanism for more than one hundred years. The kind of attempt to artificially change the apoptotic state by "missing anything, supplementing what" The idea is undoubtedly in the dead end. The "inhibition and elimination" caused by the "over-expression" of the understanding may have gone a long way.

Three years ago, Stephen Tyre, a science journalist from Berlin, Germany, wrote in the article "The Brain Plan is in Trouble", revealing the frustration of the head of the European Brain Program, Mark Ram, "although scientists all over the world have published There are tens of thousands of research papers in neuroscience, but there is no major breakthrough in understanding the basic functions of the brain". In the same year, Sally Davis, the UK's chief medical officer as a scientific leader, also showed her helplessness. "If fitness is a drug,

we all hope to use it to reduce the risk of Alzheimer's disease". However, in any case, some scholars have recently adjusted their direction and launched the "Complete Menopause Leading Cognitive Project" (PMLCP) to relieve stress and prevent shrinkage. As long as the ankles people explore do not stop, will the Augustians be reduced in the future? [1-4]

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