Redazione Calvizie (Italy)
Dec. 15, 2023

Editor's note: This English translation was done by a third party. The original digital story can be accessed here.

Post-Finasteride Syndrome: New Study

New in-depth research from the University of Milan on post-finasteride syndrome has just been published. To this is added a parallel with the related syndrome which may develop with SSRI antidepressants. Let's delve deeper into the topic.

Here is a **summary** of the main contents of **this publication.**

Twin syndromes

When a drug is prescribed, an analysis of its risks-benefits is due to assess the likeliness of obtaining benefits from the drug, compared to the risk of adverse reactions to it. Several pharmaceuticals can effectively impair our sexual function and nervous system. Persistent side effects have been reported, meaning reactions which do not cease despite cessation of the drug, for 5alpha-reductase (5α-R) enzyme inhibitors and for selective serotonin reuptake inhibitors (SSRIs), the so-called antidepressant drugs. The consequences of this are post-finasteride syndrome (PFS) and post-SSRI (PSSD) sexual dysfunction. These two clinical conditions have common aspects involving several steroids.

Neuroactive steroids

Steroids can also have local action and may also be produced by tissues not classically considered as steroidogenic. Namely, by the nervous system and, as demonstrated more recently, by the colon. Glucocorticoid hormones, sex steroids, neurosteroids, intestinal steroids and synthetic steroids are capable of affecting the nervous system. These steroids are neuroactive, meaning that they are active on the nervous system.

Steroidogenesis

Steroidogenesis is the name of the process leading to the production of steroids, which is characterized by a sequence of reactions. The final steroid is released only when all the different stages of steroid synthesis have been concluded. Thus, the final steroid is a product dependent on the enzymatic machine, in which steroidogenic enzymes are highly specific for their reactions. Steroid molecules have a pivotal role in SPF and PSSD due to their interactions with neurotransmitters and the intestinal microbiota. Researchers are trying to locate the diagnostic markers to recognize and classify patients. Great attention is paid to the alteration of intestinal microbial populations and the identification of specific bio-products derived from the microbiota.

Possible remedy

Recently, a reduction in intestinal inflammation induced on an animal model through cessation of finasteride using allopregnanolone has been observed and remarked. This could represent an interesting starting point for the implementation of steroid-based therapeutic strategies, not only for PFS but also for PSSD.

The Propecia finasteride 1 mg tablet and the Proscar finasteride 5 mg tablet.

The journey

Steroidogenesis starts from cholesterol, which is the raw material of all steroids. Within the mitochondria, cholesterol is converted into pregnenolone. From here, it can take two enzymatic paths, with the first one leading to the production of progesterone and the second to DHEA. DHEA is the precursor of androgens and therefore of testosterone, and through 5 alpha reductase (5α-R), of DHT. The same enzyme turns progesterone into DHP. But these hormones undergo a further transformation through 3 alpha oxidoreductase (3α-HSOR). DHP therefore becomes allopregnanolone, or DHT 3α diol.

Thus, by inhibiting DHT, DHP and allopregnanolone are also reduced. Steroids like the latter and pregnanolone and progesterone haveneuroprotective and anti-inflammatory effects on the intestine.

The gut-microbiota-brain axis

The colon is not just a target for steroids but is also capable of synthesizing progesterone, testosterone and their active metabolites through the use of cholesterol. Research has highlighted a greater expression of the 3α-HSOR gene in the colon of rats compared to cerebral cortex. This is in accordance with the higher levels of allopregnanolone present within the gastrointestinal tract. Indeed, this steroid is capable of binding GABA-A receptors. These receptors are widely expressed in the gastrointestinal tract.

The gut-microbiota-brain axis is the result of cooperation between the endocrine, nervous and immune systems. The intestinal microbiota basically acts like a virtual endocrine organ. The levels of neurosteroids in the brain vary in germ-free mice and pathogens-free mice. Sex steroids also affect gut bacterial communities and castration affects the steroid environment within brain and gut, with differences depending on sex. Overall, these observations support a close link between steroid molecules and the intestinal microbiota in the regulation of the gut-microbiota-brain axis.

The collaterals of anti-DHTs

Finasteride and dutasteride are two of the main 5α-R inhibitors. Treatment with these drugs has been associated with the onset of several side effects. Particularly, the less beneficial ones are linked to sexual functions. Sexual adverse events have been reported in patients with benign prostatic hyperplasia treated with finasteride or dutasteride. Furthermore, observational studies e clinical reports have described similar sexual disorders in male patients treated with these drugs in the context of anti-baldness therapies.

These symptoms include decrease or loss of libido, ejaculation disorders, erectile dysfunction, testicular atrophy, orgasm disorders and hypogonadism, although not confirmed by changes within the plasma levels of T and DHT. These are associated with increased self-harm, slowdown in cognition, psychological pathology, alterations of emotional affects, depression, sleep disorders, skin rashes and metabolic abnormalities.

To counteract the side effects of anti-DHTs, supplements exist and can be used, such as Anti-Sides by Vitaminity.

Post-Finasteride Syndrome

In some users, side effects associated with treatment with finasteride may persist despite cessation of the drug. This happens regardless of the patient's age dose of the drug or duration of treatment, inducing the so-called PFS (post-finasteride syndrome).

Sexual disorders

PFS data were obtained through questionnaires in which patients suffering from PFS self-reported their symptomatology. In particular, there were reports of decreased libido, erectile dysfunction, reduced sexual arousal and difficulty in achieving orgasm.

Other disorders

Apart from these sexual issues, another study reported psychological disorders, such as decreased self-confidence, irritability or ease of going into a rage. To these, nervousness, agitation, inner restlessness, depression, desperation, sense of uselessness, suicidal thoughts, anxiety, panic attacks, and sleep disorders may add up.

Additionally, muscle problems such as spasms and muscle fasciculations, tremors, tension and involuntary muscle contraction have been reported. Chronic fatigue, weakness, ataxia, joint and muscle pain. Physical alterations: dizziness, headache, migraine, cranial pressure, decrease in body temperature. Cognitive disorders: decreased initiative and difficulty concentrating, brain fog, forgetfulness or loss of short-term memory, loss of train of thought or reasoning, babbling or stumbling over words.

Clinical studies

Only a few studies have evaluated these symptoms clinically. These studies have confirmed a compromised sexual function in patients suffering from PFS. Even serious cases of erectile dysfunction have been acknowledged.

For example, impairment of sexual function was confirmed in 25 patients with PFS. Furthermore, another study conducted on 16 patients with PFS reported that 10 of them had a severe erectile dysfunction, while 6 patients had it mild-moderately. Another study on 25 subjects with a history of use of finasteride for baldness compared to 28 control subjects indicated a significant erectile difference. 16 of these patients had a vascular anomaly on penile duplex Doppler ultrasound scans. Somatosensory evoked potential anomalies of the pudendal nerve were reported in 25% of PFS patients studied.

Clinical studies confirmed the presence of depressive symptoms. The presence of a DSM-IV major depressive disorder in patients with PFS has been acknowledged. Furthermore, magnetic resonance imaging in PFS patients confirmed abnormalities in brain regions implicated in depression and sexual arousal, such as nucleus accumbens and prefrontal cortex.

Side effects involving sexuality are the most feared.

Hormonal dosages

In patients suffering from baldness, changes have been observed in the plasma levels of steroids, like a decrease of DHT and increased T and androstenedione, with the use of finasteride. In the plasma of patients with PFS, lower levels of DHP and allopregnanolone were recorded compared to that observed in healthy patients, along with higher levels of pregnanolone, DHEA and T. Further observations made in different cohorts of patients with PFS on serum levels concluded that only 9% of subjects showed no changes in T and DHT or low levels of both androgens.

The pattern in plasma does not precisely match what is observed in cerebrospinal fluid. For example, unlike the findings from liquor, plasma levels of pregnanolone are increased, while those of progesterone and T metabolites, such as DHT, 3α-diol and 17β-estradiol, are unchanged. Furthermore, the levels of allopregnanolone that had remained unchanged in the liquor show a significant decrease in plasma. These results are not surprising, because as demonstrated in many pathological or physiological conditions on different experimental models, neuroactive steroid changes that occur in the plasma do not precisely match what happens in the liquor and in the nervous system.

Different action mechanisms

Not only the levels of steroids can be altered by finasteride, but also their mechanisms of action. Therefore, patients suffering from PFS showed peculiar polymorphisms of the androgen receptor and of genes more or less expressed in genital organs. Furthermore, several genes at risk for developing PFS and several epigenetic pathways involving the 5α-R type II gene were also highlighted.

Microbiome

Finally, the main differences in bacterial colonies were found within the intestinal microbiota. These differences with healthy subjects are associated by other studies with depression and intestinal dysbiosis.

The intestinal microbiota and its role in many pathologies is one of the breakthrough medical discoveries of recent years.

The animal test

The test was executed on adult male rats, subcutaneously, with finasteride at a dose of 3 mg/kg for 21 days. Neuroactive steroid levels were assessed in plasma, liquor and in brain structures, such as the cerebral cortex, cerebellum, and hippocampus. This was done 24 hours after the last injection of finasteride or a month after cessation, to respectively simulate a chronic treatment and a suspension phase. After this treatment, few alterations could be observed. The situation after the cessation period proved different. Particularly, a reduction in progesterone, allopregnanolone, DHT and 3α-diol levels in plasma was observed, while in the liquor only DHT showed a decrease, while DHEA, T and 17β-estradiol increased.

At the intestinal level, the reduction of allopregnanolone and the increase of pregnanolone led to prevalence of an inflammatory microbiome. Among these bacteria a reduction in the Oscillospira strain stands out, which is a class of micro-organisms capable of producing short chain fatty acids like butyrate. This is an important reference indicator for screening “new generation probiotics”. Its decrease suggests a possible dysfunction in the production of short chain fatty acids in the PFS model, with possible adverse outcomes.

When the drug is suspended, the decrease in allopregnanolone levels observed in the intestine is related to an increase in IL-1β and TNF-α, serotonin and a decrease in dopamine. Treatment with this steroid significantly reduced the gene expression of these pro-inflammatory cytokines and the levels of serotonin in the colon of adult male rats.

The data of another recent study from this same team suggest that the sexual side effects of PFS are more related to a dysfunction in the central sexual control rather than to a condition of peripheral impairment.

Side effects induced by antidepressants

These drugs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline) have a number of side effects, including the most frequent ones being sleep disorders, weight gain and sexual issues. In particular, many studies have reported a high incidence of sexual side effects induced by SSRIs (about 59%), especially in patients treated for depression. The negative sexual symptomatology described after use of this class of drugs concerns both sexes. In fact, differences in symptoms have been reported: men suffer from sexual dysfunctions to a greater extent compared to women, while the latter experience this symptom more intensely.

Furthermore, women report sexual arousal disorders more frequently, while men are more likely to deficit in sexual desire and orgasm.

Stress and depression can lead to effluvia in telogen

Why these side effects with SSRIs?

It is hypothesized that these side effects of SSRIs are due to serotonergic inhibitory activity on the release of mesolimbic dopamine, which is linked to the control of sexual behaviour. As a matter of fact, dopamine promotes motivation and sexual behaviour. Studies on imaging further support the hypothesis of a link between serotonin and dopamine for explaining SSRI-induced sexual dysfunction.

In line with this hypothesis, the results achieved in male rats indicate that treatment with paroxetine is associated with a significant decrease in the activity of dopaminergic circuits located in brain areas associated with sexual performance.

Common aspects between PFS and PSSD

The same group of researchers had male rats undergo similar tests to those illustrated above for finasteride, but using paroxetine. These gave similar outcomes to the tests implemented with the anti-baldness drug. Particularly, analogue findings were obtained also on the intestinal microbiota, with development of an inflammatory microbiome.

The disturbance of sex steroid levels induced by finasteride or SSRIs would be responsible for alterations in neurotransmitters. This produces the sexual dysfunction observed during treatment, as well as the persistent sexual dysfunction which occurs in PFS and PSSD.

Noradrenaline and epinephrine

Both finasteride and paroxetine can also affect the equilibrium of norepinephrine and epinephrine levels, by acting on the enzyme involved in their conversion. In fact, as recently demonstrated, enzyme phenylethanolamine N-methyltransferase (PNMT), a responsible for conversion of norepinephrine into epinephrine, is a collateral target of finasteride and paroxetine. These drugs inhibit the enzymatic activity of PNMT in adrenal glands, consequently altering the levels of these neurotransmitters.

The balance of these two catecholamines is involved in the control of male sexual function, and in particular in the control of penile erection. Noradrenaline released in the penis induces the state of flaccidity, by contracting the trabecular smooth muscle. Indeed, in healthy men, reduction in levels of noradrenaline is associated with tumescence and penile erection, while an increase in levels of this hormone is associated with the transition from rigidity to detumescence.

It is interesting to note that noradrenaline can also influence our gut microbiota. Namely, this neurotransmitter promotes growth of Gram-negative bacteria, and in general, increases virulence and facilitates bacterial invasion. Additionally, increased noradrenaline levels reported in an experimental stroke model was associated with an alteration in composition of the microbiota.

SSRI drugs such as paroxetine also show a PFS-like syndrome.

Our considerations

PFS syndrome is much discussed, although quite rare statistically. The adverse effects of finasteride, when they occur, cease with discontinuation of the drug. However, it is still good to delve deeper into the worst cases in order to be able to resolve them and make the use of an essential drug for the fight against baldness less anxiogenic. We believe that the study illustrated

here has highlighted the role of the intestinal microbiota for explaining the phenomenon of PFS. Indeed, this disease sees a continuation of side effects even after cessation of the drug, and these can be better explained by the establishment of an inflammatory gut microbiome, which tends to remain and reproduce constantly.