A BRIEF HISTORY OF ERGOTISM: FROM ST. ANTHONY'S FIRE AND ST. VITUS' DANCE UNTIL TODAY

APSINUODIJIMO SKALSĖMIS ISTORIJA: NUO ŠV. ANTANO UGNIES IR ŠV. VITO ŠOKIO IKI MŪSŲ LAIKŲ

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SUMMARY

Key words: ergotism, St.Anthony's Fire, St.Vitus's Dance, antimigrenic drugs, history.

Objective. This review is devoted to the history and current manifestations of ergotism.

Material and methods. A review of available sources of medical, biological and historical literature, including Internet search engines (PubMed, msn.com and others).

Results. Ergotism appeared in Europe in the early Middle Ages and manifested itself in gangrenous or convulsive forms. Between 1085 and 1927 epidemics of convulsive ergotism were widespread east of the Rhine in Europe. The main features of ergotism history and its clinical manifestations are reviewed. A connection between ergotism symptoms and some of the most important Medieval demographic, historic, and social events is discussed. A short history of the discovery of antimigrenic drugs is presented. New cases of ergotism due to overuse of serotoninergic drugs used for the treatment of migraine and to important pharmacokinetic interactions are reviewed.

Conclusions. Ergotism has had a great influence on many European demographic, historic, and social events; religious movements; and art. Physicians must be aware of ergotism symptoms due to the overuse of ergot and triptan group drugs and to the important interactions with macrolides and HIV-protease inhibitors.

SANTRAUKA

Reikšminiai žodžiai: apsinuodijimas skalse, Šv. Antano „ugnis", Šv. Vito „šokis", antimigreniniai vaistai, istorija.

Darbo tikslas – apžvelgti apsinuodimų skalse istoriją, pagrindines intoksikacijos formas, skalsių alkaloidų savybes, antimigreninių vaistų kūrimo etapus.

Apsinuodijimai skalse (ergotizmas) Europoje pradėti registruoti 9 amžiuje, pradėjus naudoti maistui ruginę duoną. Iki pat 20 a. apsinuodijimai pasireikšdavo masiniais protrūkiais gangrenine arba traukuline forma. Dėl skalsės alkaloidų imunitetą slopinančių savybių, intoksikacijos turėjo neigiamą poveikį Europos demografijai maro epidemijų metu. Skalsės alkaloidų haliucinogeninės savybės turėjo neabejotiną įtaką „raganų medžioklei" viduramžiais ir įvairių religinių judėjimų atsiradimui renesanso laikotarpiu.

Nustačius ligos priežastį, iš skalsės išskirti gryni alkaloidai, vartojami migrenai ir kitoms ligoms gydyti. Nustačius serotonino reikšmę migrenos patogenezėje ir skalsės alkaloiodų struktūrą, buvo sukurti triptanai – nauji veiksmingi vaistai migrenai gydyti.

Pastaruoju metu padažnėjo ergotizmo atvejų dėl piktnaudžiavimo antimigreniniais preparatais bei kliniškai reikšmingos farmakokinetinės sąveikos su HIV-proteazės inhibitoriais ir makrolidais. Gydytojai turėtų žinoti tokios sąveikos ir piktnaudžiavimo anmigreniniais vaistais reikšmę.

Introduction

Ergot of rye (*Secale cornutum*) is a disease of cereals that is caused by the fungus *Claviceps purpurea*. In fact, the name "ergot" comes from the French word "argot", which means spur [1]. There are 32 recognized species of ergot. The fungus produces alkaloids (mycotoxins) that cause ergotism in humans and animals. Six of the most important pairs of ergot alkaloids have been iso-

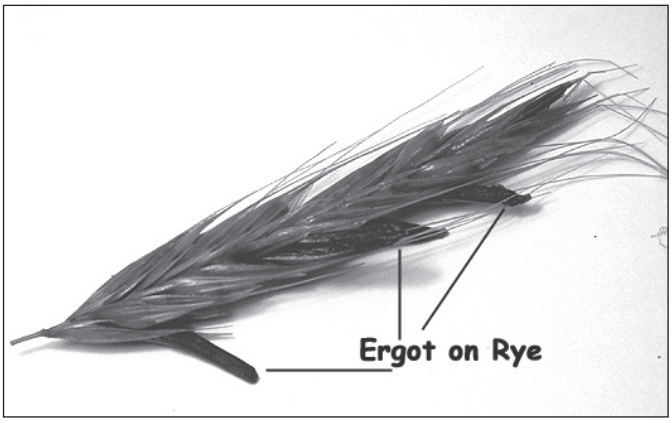

Fig. 1 Ergot on rye spike

lated. Only L-enantimers (ergotamine, ergocristine, ergometrine, etc.) possess significant vasoconstrictive and neurotoxic activity. They all are derivatives of lysergic acid [2].

Susceptibility to infection among crops increases with any condition that prolongs flowering, so, cool, wet weather and wet soils favor germination of the ergot bodies.

The proportion of the compounds produced vary with the species. Thus, a person who has lived through ergot poisoning once may experience different symptoms another time.

Ergotism and its clinical manifestations

Poisoning attributed to ergot of rye is referred to as ergotism. There are a couple of very early references to ergot. It was probably the "noxious pustule in the ear of grain" noted on an Assyrian cuneiform tablet of around 600 BC. One of the sacred books of the Parsees (400 BC to 300 BC) mentions "grasses that cause pregnant women to drop the womb and die in childbirth." In spite of this fact, rye was not eaten by ancient Greeks and Romans, so there are no undisputed references to ergotism in the literature of that period. It was not until the Christian era began and rye was introduced into western Europe that written accounts of ergot poisoning began to be found. A very early outbreak of ergotism was documented in the Rhine Valley in 857 [1].

Ergotism has two forms: gangrenous (St.Anthony's Fire) or convulsive (St.Vitus' Dance).

In gangrenous ergotism, people experience nausea and pain in the limbs. Quite often bodily extremities turn black, dry, and become mummified, causing the infected limbs to spontaneously break off at the joints. Spontaneous abortion also occurred frequently. The initial burning sensation led to the Latin name "ignis sacer", which means Holy Fire. This human malady was

Fig. 2 Ergot sclerotia

so horrible that in 1093 a religiuos order, the Order of Hospitallers of St. Anthony, was founded in southern France to help those afflicted. Since St.Anthony was the patron saint, the malady was named St.Anthony's Fire. Monks built over 370 hospitals and those who came often did find relief from ergotism. This was probably due to the absence of rye bread from the patients' diet during their care in the hospital [1].

Convulsive ergotism is characterized by nervous dysfunction – painful seizures and spasms simulating convulsions. In some cases this is accompanied by hallucinations, mania or psychosis. This form of ergotism has been suggested as a possible scientific explanation for some of the outbreaks of dancing mania, a phenomenon that occurred primarily in mainland Europe from the 14th to the 17th centuries and that was characterized by mass hysteria, uncontrolled ecstatic body movements, convulsions, and hallucinations. An Italian variant was known as tarantism because the sick were believed to have been bitten by the tarantula spider, for which the only cure was thought to be frenetic dancing to certain music, which supposedly dissipated the "poison" from their blood.

In order to exorcise the demons thought to be causing the mania, people often prayed to St. Vitus (martyr, died c.303) from Sicily, who became the patron saint of dancers. The term „St. Vitus' Dance", however, refers to a syndrome known as Sydenham's chorea, which is totally unrelated to manic dancing. Ergotism was probably not the only cause of dancing mania - other factors triggered by adverse social circumstances were also involved [3].

The gangrenous and convulsive forms of ergotism could occur concurrently (mixed forms). The reason

for the prevalence of gangrenous ergotism west of the Rhein River and of convulsive ergotism east of the river is not clear to this day.. Most probably, it depended on the species of ergot and, consequently, qualitative/ quantitative content of mycotoxins.

The last reported outbreak, which caused more than 200 cases and 4 deaths, occured in 1951 in Pont St.Esprit, although this claim seems to be controversial.

Disclosing the causes of ergotism

W. Thelius, a German physician, gave an account of an epidemic that raged in the Kingdom of Hesse in 1596. He was one of the first to attribute the cause of ergotism to grain. In 1670, a French physician, Dr.Thuillier, determined that ergotism wasn't an infectious disease. He also noted that it occurred in poor rural areas rather than in highly populated, unsanitary urban areas. Looking for the cause of ergotism he determined the source to be food. He noticed the ergots in a field rye. The peasants were eating the ergot rye in the form of bread. Thuillier also noticed that in years that the cockspurs filled the rye heads that Holy Fire raged through the countryside and hundreds died. But farmers didn't believe him and considered ergot to be harmless [1].

In 1853, Louis Rene Tulanse, an early mycologist, worked out the life cycle for the ergot of rye. Tulanse performed numerous experiments and concluded that the ergot was a fungus. He also knew that ergot had been used by alchemists in their potions to hasten child birth. These ergots were not to be eaten by humans or animals because they contained poisonous alkaloids. So, the cause of ergotism was disclosed at last. According to modern psychopharmacology, ergotism (especially convulsive) may represent serotonergic overstimulation of the CNS (i.e., the serotonin syndrome)[4].

Ergotism, bubonic plague and other historical events

Europe during the high Middle Ages, the 1100s-1200s, was in a period of relatively good health and population growth. However, this ended between 1348-1350, when a major epidemic of the bubonic plague struck. It is estimated that 1/3 of Europe's population died as a result of the plague. Although the death toll on this occasion was high, a depression in the population of Europe lasted untill 1490. This puzzled historians because even with such a high number of deaths, population recovery should have occurred by the next generation, unless other factors were involved. Matossian believed that as ergot seriously weakened the immune system, consumption of grains infected with ergot increased the mortality. During the plague men were often forced to consume substandard food that more than likely was contaminated with mold. It was known that after the plague, the winters were unusually cold. In those years rye would be more likely to survive than wheat. Ergot poisoning is also known to reduce fertility and cause spontaneous abortions. Recovery of population had stopped almost for a century [5].

Ergotism and witchcraft

When large numbers of people came down with the symptoms of ergotism, especially convulsions and hallucinations, many in the 16th and 17th centuries concluded that they must have been victims of witchcraft and witches were blamed for the symtoms. Some contemporary researchers have even examined the possible role of ergotism in the Salem, Massachusetts witch trials of 1692. Witch hunts hardly occured where people did not eat rye [5, 6].

Ergotism and religious movements

In the 1740s, the so called Age of Rationalism, ergot symptoms became a mark of holy, not demonic possession. Visions, trances and spasms were read as religiuos ecstasy. Chronic intake of ergot, resulting in a wide variety of neuropsychiatric and vascular symptoms, is shown also to coincide with various mystical movements, such as the early Pietist movement in Germany, Sabbateanism and Chasidism [7]. The latest movement is directly related to LSD (Lysergic acid diethylamide). LSD became famous in the 1960s through the notoriety of two Harvard psychology pro-

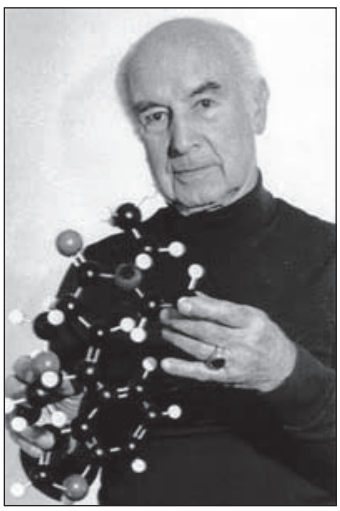

Fig. 3 Albert Hoffman with a model of LSD molecule

fessors, R.Albert and T.Leary, who proposed the motto "turn on, tune in, and drop out" and who accelerated the psychodelic drug movement in middle class America. Careless experiments with college students on psychoactive drugs were enough cause to have both of them booted out of Harvard. In 1966 Leary organized the League of Spiritual Discovery, for which LSD was a sacrament. The US government convicted Leary of possession of LSD and marijuana, but he esacaped to Algeria and spent several years there in prison. Albert was trained by a guru in India, and under a new name, Bab a Ram Dass, created a following that seeks a "meditative high".

Ergotism in art

Strange human behaviour impressed artists of the Middle Ages and later the Renaissance. M.Grunewald, who painted in the Rhine valley at the time of Albert Durer and Lucas Cranach, despicted figures with abnormal postures simulating focal and generalized dystonia. It is likely that patients with chronic ergotism modelled for M.Grunewald and his paintings are the first artistic representations of dystonia. Hyeronimus Bosch in his St.Anthony's triptych (and in "The procession of the cripples") painted people with amputated and mummified feet; a strange figure – half human, half vegetable; and an egg-shaped structure belching smoke and flame. Actually, the odd vegetable creature is painted in the shape of a mandrake root. Mandrake was the herb used to stanch the feverish pains of St.Anthony's Fire. The egg-shaped building is exactly in the shape of an apothecary's retort – the distillery used to reduce medicinal herbs [8-10].

This topic – the temptation of St.Anthony – was used many times by numerous later painters, including S.Dali and others.

Fig. 4 Saint Anthony

Fig. 5 Saint Vitus

Isolation of ergot alkaloids

Attemps were made from the mid - 19th century onwards to isolate the active alkaloids from ergot. Ergotoxine, isolated by G.Barger and H.Dale in 1906, was initially thought to be a pure substance, but later was found to be a mixture of four alkaloids. The first of these alkaloids, ergotamine, which is still used for the treatment of acute migraine, was isolated by A.Stoll in 1918. Ergometrine was isolated by C.Moir and H.W.Dudley in 1935. In 938, A.Hoffman and A.Stoll, derived d-lysergic acid diethylamide (LSD). It was thought to be relatively uninteresting until A.Hoffmann accidentaly ingested a small quantity of the drug. In 1943, A.Hoffmann synthesized dihydroergotamine, marketed for the treatment of hypertension and later – for migraine [1]. Sandoz chemists discovered yet another important antimigraine drug, methysergide. Used for daily preventive therapy rather than abortive treatment of migraine, methysergide is a serotonin antagonist, whereas ergotamine is a serotonin agonist. The main limitations for the use of ergot alkaloids is the relative high incidence of side effects. Overuse is associated with the development of a chronic drug rebound headache and risk of ergotism. Methysergide is capable of causing fibrotic complications. Other ergot drugs have been suspected of having this potential as well [11-12].

The ergot alkaloids are structurally related to the biogenic amines, serotonin, norepinephrine and dopamine. Because of their structural similarities with the neurotransmitters, they exert wide-ranging effects on adrenergic, dopaminergic and serotoninergic receptors.

Several clinical and experimental observations confirm that serotonin has a major role in producing or maintaining a migraine attack. A new era in antimigraine drugs began in 1973 with efforts to synthetize more selective serotonin agonists among triptans. The first – sumatriptan – was introduced in 1991 [11].

Ergotism today

Overuse of ergot alkaloids for the treatment of acute migraine is associated with the development of a chronic drug rebound headache and risk of ergotism. So, general practitioners and physicians should be aware of the possible ergotism arising from prolonged or excessive use of ergot medicines [13].

It is also known that some drugs, including macrolides and antiretrovirals (used for the treatment of AIDS patients) interfere with ergotamine metabolism [14-16]. These agents are strong cytochrome P-450

(CYP3A4) inhibitors. Drug interactions may be most apparent when patients are stabilised on the affected drugs (ergotamine, triptans) and the CYP3A4 inhibitor is then added to the treatment regimen. Thus, ergot concentrations are probably increased to toxic amounts because HIV-protease inhibitors and macrolides block ergotamine metabolism [13-14, 16]. Clinically, it manifests in painful sensations in the legs, headache due to vasospasm of cerebral arteries, sometimes abdominal pain, even with the necrosis of intestines. Multiple cases of vasospastic stenoses and occlusions were demonstrated by duplex sonography or angiografic investigation. Doctors should be aware of these harmful interactions, and any administration of ergot alkaloids (or triptans) should be discontinued when antiretroviral therapy is started in patients with HIV infection [16].

Ergometrine and methylergometrine are still used for the treatment or prevention of postpartum haemorrhage and to accelerate involution. Although comparatively small quantities of ergot alkaloids appear in milk, neonates are especially sensitive to them. Sometimes these alkaloids are associated with severe complications, including convulsions and apnoe. Ergometrine is shown to lower prolactin levels, which may decrease lactation. So, exercise caution when these drugs are administered to a nursing woman [18].

Conclusions

Ergotism has had great influence on European demography as well as many historical, political, and social events, religious movements, and art. Physicians must be aware of ergotism symptoms due to the overuse of ergot alkaloids and antimigrenic drugs of the triptan group as well as important interactions with macrolides and HIV-protease inhibitors.

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