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Volume 2 • Issue 6 • 2018

Scientia Ricerca

Review Article

Current Opinions in Neurological Science

ISSN: 2575-5447

Alzheimer's: Do Anti-Herpetics Reduce the Risk of Dementia and if so, Why?

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Received: November 07, 2018; **Published:** November 21, 2018

Abstract

It is always of critical importance to scrutinize biomedical studies for accuracy, especially those even suggesting benefits of novel applications for widely used medications. An example is a 2018 retrospective Taiwanese study in which Tzeng claims that patients with HSV infections 'may have' a 2.56-fold increased risk of developing dementia. Furthermore, and more appropriate to the title of his paper (*Anti-herpetic Medications and Reduced Risk of Dementia in Patients with Herpes Simplex Virus Infections-a Nationwide, Population-Based Cohort Study in Taiwan*), Tzeng claimed that the usage of anti-herpetic medications was associated with a decreased risk of dementia. However imperfections in the study suggest the need for a more controlled study. For example, in the HSV-group merely 13.7% (1147 in 8362) did not receive anti-herpetic medications [1].

Volume 2 Issue 6 November 2018

Introduction

In January of 2006, Catherine Helmer first published a similar study: *Herpes simplex virus, anti-herpetic medication, and dementia: Results from the three-city population-based cohort*. But Helmer., *et al*. concluded that their results regarding anti-herpetic medications were "not significant" for lessening dementia. Helmer presented this paper once again, this time for *Alzheimer's & Dementia* in July, 2015 [2].

As such a high seroprevalence for Herpes simplex type 1 exists in populations at large, both the Tzeng and Helmer studies mention reactivation of the virus as being important for active disease. According to WHO, globally, an estimated two-thirds of the population under 50 are infected with Herpes simplex virus type 1, and that ratio only goes upwards with increased age. Concurrent infections, such as viral upper respiratory tract infection or other febrile diseases, can cause outbreaks. Reactivation due to other infections is the likely source of the historic terms "cold sore" and "fever blister."

This concept of reactivation through existing systemic disease is therefore critical to the understanding of Herpes simplex virus type 1. In 1896 German physician Paul Unna developed a way to differentiate herpes from syphilis under a microscope [3]. This observation was important because previously it was not possible to identify the difference between herpes and syphilis since they are often

concurrent. The notion that Herpes simplex might have been caused by a living infectious agent resulted from the 1912 work of Grüter, who inoculated the cornea of a rabbit with material derived from corneal herpes in man [4].

This produced a typical keratitis, transmissible in series. Later on, in 1919, the scientist Lowenstein confirmed that herpes was an infectious disease, extending these findings to herpes of the skin and mucous membranes. Lowenstein showed that not only corneal herpes, but also simple herpes and the symptomatic herpes accompanying diseases such as tuberculosis produced a specific keratitis when inoculated in the cornea of a rabbit. And with considerable regularity, Lowenstein noticed, herpes could be passed from rabbit to rabbit [5]. Following Lowenstein, Kooy confirmed the latter's findings of the transmission of the "virus" of febrile herpes. Kooy carried out a series of inoculations on rabbits, using the contents of herpetic vesicles [6].

He inoculated the cornea of rabbits with herpetic dendritic keratitis, and herpes labialis in febrile disease. Then he described his herpes culture's morphology and staining in detail. Much to his own surprise, what Kooy isolated was not a virus at all. Rather from twenty-five inoculations upon the cornea he succeeded twenty-two times in culturing a polymorphic, cell-wall-deficient, viral-like microorganism belonging to the *Mycobacteriaceae*. Mycobacteria are a genus of the Actinobacteria, given their own family, the *Mycobacteriaceae*. Over 190 species are recognized in this genus. This genus includes pathogens known to cause serious diseases in mammals, including tuberculosis (*Mycobacterium tuberculosis*) and leprosy (*Mycobacterium leprae*) in humans. In direct culture from herpes labialis (cold sores of the lip), Kooy again succeeded three times in culturing these same Mycobacteria.

In animals with a general diseased condition, these microorganisms were also isolated three times from the blood and spleen. In general, several mycobacterial forms were found in the same culture; although, at times, pure cultures of one form were observed. All of the forms could be demonstrated in smear preparations of conjunctiva secretion and corneal infiltration. The organisms flourished at 37°C, as well as at room temperature, were more aerobic than anaerobic, and the cultures could be transferred by inoculation from one rabbit's cornea to another. The case for Alzheimer's and many of the dementias as a sub-clinical, underlying Mycobacterial disease has previously been made [7-10].

Enter Acyclovir (Zovirax®)

Prescription antiviral (anti-herpetic) medicines approved for the treatment of both types of herpes simplex include acyclovir, famciclovir, and valacyclovir. However, since they were known to have activity against viruses, no studies for activity against bacteria or mycobacteria were included in their package inserts –nor looked for in any Western studies. Acyclovir (Zovirax®) for example was an anti-viral, so why would anyone look further?

The discovery of acyclovir as an antiviral agent, and what made its "career" as an antiherpes drug was purported to be its selective activity against herpes simplex virus (and later varicella-zoster virus) – all due to a specific recognition by these viruses thymidine kinase (TK). The antiviral activity of acyclovir was discovered by Peter Collins (Wellcome) in Beckenham, UK, but the fact that it was recognized as substrate by the viral TK stemmed from Gertrude Elion and her colleagues at Burroughs Wellcome in Research Triangle Park (RTP). At that time (late 1970s), there was a high need for the systemic treatment of HSV infections, and this explains why Wellcome developed and scrutinized acyclovir solely for the treatment of HSV.

An anti-viral or more?

When she worked on the drug for HSV, Elion determined exactly how and why it worked. To Elion, Acyclovir, marketed as Zovirax®, interfered with the replication process of the herpesvirus –and only the herpesvirus –proving that drugs can be selective. That is, until a Polish study would one day prove this wrong.

And so while Western literature remained silent about acyclovir as having anything but anti-viral activity, this Polish study found that acyclovir actually had activity against *Pseudomonas aeruginosa* and *E. coli* –two out of only 4 bacteria used in this study that acyclovir was tested against. The mycobacteria were excluded [11]. Gertrude Elion hypothesized that what made acyclovir an antiviral

agent and antiherpes drug was its selective activity against herpes simplex virus as being due to a specific recognition by herpes's viral thymidine kinase (TK). Yet she never tested the drug on bacteria or mycobacteria. *Mycobacterium tuberculosis* has its own thymidine kinase, crucial to its pathogenicity [12]. But acyclovir's activity was never tested against this.

Similarly, by 1949, Gertrude had synthesized a purine that inhibited growth in mouse leukemia, which Joseph Burchenal at Sloan Kettering Institute in New York used to treat four patients with chronic granulocytic leukemia, two of whom went into remission. This was the forerunner of 6-mercaptopurine, which continues to be effective in some cancers. Yet good activity of 6-mercaptopurine against *M. tuberculosis* has also been recently reported by Greenstein [13].

An example of why anti-virals should not be assumed to be just for viruses until confirmed is below. In one assay study of 1,2,3 triazole derivatives, [14] not only were they superior in their anti-HSV-1 activity to acyclovir, but these same triazole derivatives were described by the investigators as having "potent activity" against HSV-1. https://www.ncbi.nlm.nih.gov/pubmed/21376603

However, in a 2017 study of related "anti-viral" triazole derivates, 25 exhibited "promising" anti-TB activity [15]. And this study merely confirmed an investigation on 1,2,3-triazole derivatives as anti-tubercular agents done two years earlier [16].

Acyclovir is a synthetic purine nucleoside analog derived from guanine. Nucleosides are well known for their antiviral and anticancer properties. In addition to this, they have recently shown great potential against *Mycobacterium tuberculosis*, [17] though this is not a new finding. In 2003, Pochet *et al* reported a comparative study of purine and pyrimidine nucleoside analogues as inhibitors of the mycobacterial enzyme thymidine monophosphate kinase (TMPKmt), believed to be a potentially attractive target for the design of a novel class of anti-tubercular agents [18].

An Expert Weighs in

A pioneer in antiviral research, Erik De Clercq, is quite familiar with the discovery of acyclovir as an antiviral agent. De Clercq began his medical career in 1966, received his certification in Clinical Pathology in 1971, and his Ph.D. the following year. Over his prodigious career, Dr. De Clercq's research focused on the development of new therapies, and in particular, the development of new agents against viral infections. He is widely recognized for his seminal work in the field of nucleotide analogs, which were the first broad-spectrum antivirals, and sparked a new era in antiviral development. Dr. De Clercq was also Editor-in-Chief of the journal *Antiviral Research* from1981 to 2011.

When asked specifically regarding whether acyclovir and other anti-herpetics might have activity against *M. tuberculosis*, Dr. De Clercq said "I am sure that acyclovir and some other antivirals should have some activity against some bacteria, including *M. tuberculosis*, but this does not make them useful for the treatment of such infections" [19]. [Personal communication 10/10/2018] Yet, at the same time Dr. De Clerq admitted that "In the whole context, the antimicrobial potential of acyclovir and valacyclovir, if any, did not receive due attention". In other words, such testing was never done. So how would one know whether TB could be treated by acyclovir as well?

Mohammed Asif, who wrote in his *Development of new anti-tubercular drugs containing Benz-fused ring system* [20] that recently purine analogues have been found to possess anti-TB activity, was essentially asked the same question, specifically about acyclovir and its derivatives. Since acyclovir is a synthetic purine nucleoside analog derived from guanine, does it have activity against TB and the mycobacteria? His reply: "Chances of anti-tubercular activity for these drugs is very high. But no strong evidence and research was ever published" [21] [Personal communication 9/27/2018].

This leaves the question wide open as to whether acyclovir and the current anti-herpetic nucleoside analogs have anti-mycobacterial activity. At the present and past level of willingness to break such ground, we may never know. Certainly, almost as if by design, all of the early developers and their pharmaceutical employers made no attempt whatsoever to define the activity of acyclovir and its related

congeners against either bacteria or mycobacteria. This seems strange, no matter how air-tight their hypothesis or guess was as to why a drug, anti-viral or otherwise, does what it does.

References

1. Tzeng NS., *et al*. "Anti-herpetic Medications and Reduced Risk of Dementia in Patients with Herpes Simplex Virus Infections-a Nationwide, Population-Based Cohort Study in Taiwan". *Neurotherapeutics* 15.2 (2018): 417-429.
2. Helmer Catherine., *et al*. "Herpes simplex virus, anti-herpetic medication, and dementia: Results from the three-city population-based cohort". *Alzheimer's & Dementia* 11.7 (2015): 153.
3. Unna P Gerson. "The histopathology of the diseases of the skin". (1896).
4. Grüter W. "Experimentelle und klinische Untersuchungen über den sogenannten Herpes corneae". *Berichte über die Versammlung des Ophthalmologischen Gesellschaft. (Heidelberg)* 42 (1912): 162.
5. Löwenstein A. "Aetiologische Untersuchungen über den fieberhaften Herpes". München. Med. Wochenschr. 66 (1919): 769-770.
6. Kooy JM. "Virus of febrile herpes". Klin M. f. Augenh 66 (1921): 75.
7. Broxmeyer L. "Are the Infectious Roots of Alzheimer's Buried Deep in the Past?" *Journal of MPE Molecular Pathological Epidemiology* 3 (2017): 1-19.
8. Broxmeyer L. "Dr. Oskar Fischer's Curious Little Alzheimer's Germ". *Current Opinions in Neurological Science* 1.3 (2017): 160-178.
9. Broxmeyer L. "Alzheimer's disease –How Its Bacterial Cause Was Found and Then Discarded". *Create Space Independent Publishing Platform* (2016): 190.
10. Broxmeyer L. "Dr. Oscar Fischer's Mysterious Little Alzheimer's germ". *Journal of Alzheimer's disease* (2017): 1-3.
11. Kruszewska H., *et al*. "Search of antimicrobial activity of selected non-antibiotic drugs". *Acta Poloniae Pharmaceutica* 59.6 (2002): 436-439.
12. Munier-Lehmann H., *et al*. "Thymidylate kinase of Mycobacterium tuberculosis: A chimera sharing properties common to eukaryotic and bacterial enzymes". *Protein Science : A Publication of the Protein Society* 10.6 (2001):1195-1205.
13. Greenstein RJ., *et al*. "Unanticipated Mycobacterium tuberculosis complex culture inhibition by immune modulators, immune suppressants, a growth enhancer, and Vitamins A and D: clinical implications". *International Journal of Infectious Diseases* 26 (2014): 37-43.
14. Jordão AK., *et al*. "Synthesis and anti-HSV-1 activity of new 1,2,3-triazole derivatives". *Bioorganic & Medicinal Chemistry* 19.6 (2011): 1860-1865
15. Rode ND., *et al*. "Synthesis, biological evaluation, and molecular docking studies of novel 3-aryl-5-(alkyl-thio)-1H-1,2,4-triazoles derivatives targeting Mycobacterium tuberculosis". *Chemical Biology & Drug Design* 90.6 (2017):1206-1214.
16. Shaikh MH., *et al*. "1,2,3-Triazole Derivatives as Antitubercular Agents: Synthesis, Biological Evaluation and Molecular Docking Study". *MedChemComm* 6 (2015): 1104-1116.
17. Ferrari V and Serpi M. "Nucleoside analogs and tuberculosis. New weapons against an old enemy". *Future Medicinal Chemistry* 7.3 (2015): 291-314.
18. Pochet S., *et al*. "Comparative study of purine and pyrimidine nucleoside analogues acting on the thymidylate kinases of Mycobacterium tuberculosis and of humans". *ChemBioChem* 4.8 (2003): 742-747.
19. Personal communication 10/10/2018: Broxmeyer and De Clerq.
20. Asif M. "Development of new Antitubercular drugs containing Benz-fused ring system". *Organic Chemistry* 9.3 (2013): 102-114.
21. Personal communication 9/27/2018: Broxmeyer and Asif