Subacute myelo-optic neuropathy, Alzheimer's, autophagy, cancer, and SNPs: The curious case of clioquinol continues

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One of the first mass-produced drugs, clioquinol (5-chloro-7-iodo-quinolin-8-ol), was developed as a topical antiseptic. For many years, it was considered safe and efficacious. However, an outbreak of subacute myelo-optic neuropathy, or SMON, a debilitating disease caused by clioquinol, and almost exclusively confined to Japan, resulted in a ban of the drug. Interest in clioquinol was renewed after positive effects of the drug in Alzheimer's disease models were reported. A decade later, novel data brought additional questions and hypotheses that offered new promise. In 2011, clioquinol was identified as an inducer of autophagy, and in 2016, as a blocker of cAMP-efflux possibly mediated by two ABC transporters: ABCC4 and ABCC11. A set of SNPs that dramatically reduce transporter function in ABCC4 and ABCC11, and almost exclusively confined to the Japanese population, suggests a possible connection between SMON, clioquinol, and the transport of the nucleotide-like drugs. A "beneficial role" of selected SNPs in breast cancer, also reported only for Japanese women, may indirectly support our hypothesis that highlights the role of cyclic nucleotide efflux in the apoptotic evasion of cancer. The effect of clioquinol on CREB phosphorylation and a proposed role of CREB phosphorylation in Alzheimer's disease may indicate a previously unappreciated mechanism, whereby clioquinol may affect synaptic plasticity by altering the cAMP-dependent signaling pathway.