The onchocerciasis parasite showing signs of resistance

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Onchocerciasis is an infection caused by Onchocerca volvulus, a parasite nematode worm transmitted to humans by a species of black fly of the Simulium genus whose larvae develop in fast-flowing rivers. Infected subjects suffer not only from severe skin lesions but also eye damage that can lead to irreversible loss of sight, hence the name 'river blindness'.

A huge majorityy -- 99% --of the 37 million people infected by the parasite live in SubSaharan Africa. Ivermectin, a medicine capable of killing the parasite embryos (the microfilariae) circulating in the organism of patients and temporarily interrupting the nematode's reproduction, is the only treatment used for onchocerciasis control. Since 1995, the African Programme for Onchocerciasis Control (APOC) has been covering 19 of the continent's 28 countries hit by the disease. Access to this treatment is possible for 70 million people and has significantly diminished the onchocerciasis-induced morbidity.

However, the doubling of cases of infection in certain communities of Ghana between 2000 and 2005, in spite of annual treatments, created fear of the emergence of ivermectin-resistant strains. Such apprehension appears particularly justified in that a high degree of therapeutic cover is achieved during mass distribution campaigns and hence only a tiny part of the parasite population targeted remains unexposed to drug treatment pressure.

Since 1994, a team of IRD researchers, working jointly with Cameroon

researchers and others from McGill University of Montreal, has been monitoring a cohort of Cameroon patients benefiting from repeated treatments with ivermectin. Regular parasite sampling from these subjects was performed over a 13-year period in order to determine the changes in the genetic structure of Onchocerca volvulus populations. Each occasion involved measurement of the genotype frequency of heterozygotes and homozygotes for the gene coding β-tubulin, a protein involved in the organization of the parasite's cells.

The team focused on this particular gene because it acts as a marker of resistance to ivermectin in other nematode species parasitic on cattle. As a control, they monitored the changes in genotype frequency of two other genes, known for their high evolutionary stability over time. The proportion of homozygotes and heterozygotes for these two genes remained stable throughout the investigation, but the situation was completely different for the β-tubulin gene. Between 1994 and 1998, the percentage of parasites showing a genotype homozygous for this gene fell from 79 to 31% in subjects receiving quarterly treatment with ivermectin. At the same time, the proportion of heterozygous genotypes changed in the opposite sense, rising from 21 to 69%.

These results could be the sign of adaptation of nematode worm populations to repeated treatments using this drug. The research team inferred that the parasites showing a genotype homozygous for β-tubulin are more susceptible to it. As courses of treatment progressed, they would therefore gradually disappear, to the benefit of the more resistant heterozygous strains. Ivermectin's effect on microfilariae, other than its direct one, is to prevent them from leaving the uterus of adult worms, for several months after treatment: this is its embryostatic effect. Post-treatment, there were more microfilariae in the uterus of homozygous female parasites than in those of heterozygous females.

This could mean that, in the latter, the microfilariae succeed in leaving

the uterus, as they usually do in the absence of treatment, and therefore that the embryostatic effect of ivermectin would be diminished. Contrary to the effect anticipated, the repeated exposure to treatments could in this way select those worms more able to keep up the production of new generations. Nevertheless, the drug's direct action on the microfilariae appeared not to change, and hence, for the moment, there is no reason to call into question the current control strategy against the disease based on annual treatments with ivermectin.

Affirmation of the results requires further investigations, starting from new cohorts subjects infected by Onchocerca volvulus who have not yet been treated with ivermectin. This type of approach should bring more information on the risks of the parasite's resistance to this drug. If such risks were confirmed, then the whole onchocerciasis control strategy would probably have to be revised. Nevertheless, for many years to come, ivermectin could well remain the sole drug applicable for mass treatment in measures to control river blindness.

Source: Institut de Recherche Pour le Développement