# Seizures as a rare adverse effect of chloroquine therapy in systemic lupus erythematosus patients: a case report and literature survey

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Aside from corticosteroids and immunosuppressants, chloroquine is one of the fundamental pharmaceuticals used in systemic lupus erythematosus (SLE) therapy. Its mechanism of action is not entirely understood, however, scientists' suppositions concern its pleiotropic nature, including stabilization of lysosomal enzymes, inhibition of antigen-presenting cells and T lymphocyte stimulation as well as blocking of the pro-inflammatory cytokine cascade, and photoprotection [1]. Also, it belongs to antimalarials, which are thought to be safe, well tolerated and effective in treatment of SLE and other inflammatory diseases [2–4]. According to research, antimalarials substantially reduce activity of the disease in more than 50% of patients and only 15% of patients discontinued antimalarial therapy because of side effects [5]. The most important adverse effects include irreversible retinopathy and ototoxicity, neuromuscular, gastrointestinal and hematopoietic reactions as well as hyperpigmentation and electrocardiography (ECG) changes [3]. Also, in rare cases, chloroquine can cause epileptic seizures, which is the subject of this paper.

A 49-year-old female patient had been diagnosed with SLE according to the American College of Rheumatology (ACR) criteria based on the following symptoms: arthralgia for 6 months, general weakness, raised temperature, loss of the body mass (about 10 kg in the 2 previous months), sunlight sensitivity, skin lesion of discoid lupus, leukopenia, presence of anti-nuclear antibodies (ANA) 1 : 2560 and decreased complement levels of C3 and C4. The patient started a therapy of 32 mg/day methylprednisolone, and after 2 weeks a dose of 250 mg/day chloroquine was added. Improvement of her general state, muscle strength, appetite and lessening of arthralgia were noted. Except for stomach ache, the patient did not complain about other side effects.

After one month of chloroquine therapy, with no previous history of such symptoms, the patient developed epileptic seizures lasting for 24 h. The seizures were of the complex partial type, and manifested themselves through an abnormal contact and involuntary movements of the upper limbs. The patient was rapidly admitted to the Neurological Department of the Medical University of Lodz, where computed tomography (CT) and magnetic resonance imaging (MRI) were performed (no pathological changes noticed). She also underwent an electroencephalography (EEG) examination, which showed significant changes of right-side-predominant, generalized discharges of slow and sharp waves and spikes. During hospitalization, the patient was administered valproic acid which achieved a therapeutic blood level. Chloroquine was ceased. Based on the patient's medical history and results of additional testing it was assumed that the epileptic seizures were most likely provoked by this drug. Up until now, the patient has had no more episodes of epileptic seizures. The patient remains under the care of a dermatologist and a neurologist and takes 900 mg/day of depakine and systemic corticosteroids.

Seizures, as an adverse effect of chloroquine therapy, occur very rarely [6]. A significant part of cases in the literature refer to patients with malaria [7, 8], leprosy [9] and chloroquine poisoning [10, 11] as Tristano *et al.* noticed [12]. Seizures were also noted among patients with mental diseases [13]. Medical literature presents only single cases of epileptic seizures in SLE patients after administration of chloroquine [6, 12] or hydroxychloroquine [14]. It is important to consider any previous episodes of seizures during analysis of these cases. Seizures induced by chloroquine are probably connected with the inhibition of GABAergic neurotransmission [15].

Malcangi *et al.* [14] presented the case of a 17-year-old female patient (diagnosed with SLE), who developed tonic-clonic seizures after 2-week hydroxychloroquine

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therapy (200 mg/day). In contrast to the previously mentioned case, the patient had a history of complex partial type seizures with prodromal aura, loss of consciousness, brief cessations of respiration, cyanosis, urine and fecal incontinence and a subsequent postictal state. The EEG performed after seizures (abnormal bisynchronous waves of the frontotemporal lobes) was congruous to those of previous seizures.

Tristano *et al*. [12] described a 14-year-old female patient suffering from SLE, who presented tonic-clonic seizures during 3-week chloroquine therapy at a dosage of 500 mg/day. She (and her family) had no history of seizures and her EEG pattern was not objectionable.

Another case was described by Luijckx *et al*. [6] which refers to a 28-year-old female with discoid SLE. She was admitted to the hospital due to tonic-clonic seizures after 6-week chloroquine treatment at a dose of 200 mg/day. She had no history of previous seizures, however, the patient's brother (untreated) had developed tonic-clonic convulsions in the past. The patient's cerebrospinal fluid (CSF) examination was normal, while her EEG showed postictal abnormalities.

In all cases above, imaging scans were normal and seizures ceased after chloroquine therapy was stopped, which suggests its role in induction of seizures.

To summarize, chloroquine treatment was the most likely cause of seizures in the case presented, according to the patient's medical history and examinations performed: no seizures in the past, occurrence of convulsions after initiation of chloroquine therapy, no seizures after ceasing the drug, EEG changes and subsequent normalization and no changes in imaging scans. Based on these data, we could assume the presence of a neuropsychiatric form of SLE (NPSLE) [12, 14], which occurs in 64.44% of patients with SLE. Frequency of seizures in this type is estimated at about 10.67% [16].

Despite chloroquine's reputation of being a highly safe drug, it is necessary to emphasize that it should be used very cautiously in all SLE patients as well as in those who suffer from other diseases, including rheumatological, mental and neurological disorders.

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## Conflict of interest

The authors declare no conflict of interest.

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