CLINICAL AND THERAPEUTICAL ASPECTS OF GINGIVAL OVERGROWTHS INDUCED BY ANTICONVULSIVE DRUGS (PHENYTOIN)

Mihaela Diana GHEBAN1, Diana CRISTEA2, Liliana Gabriela HALIŢCHI1, Cătălina GÎRBEA1

1 Assist. Prof., PhD, „Apollonia” University of Iaşi, Romania
2 Univ. Assist., PhD student, „Apollonia” University of Iaşi, Romania
Corresponding author: Mihaela Diana Gheban; e-mail: diana.gheban@yahoo.com

Abstract

Hypertrophic drug-induced gingivites aroused a special interest from the part of researches, if considering the quite numerous studies devoted to the clinical aspects and treatment of such pathological gingival manifestations. In this context, the first observation to be made is the absence of an unanimous position as to their treatment, starting from the prophylaxy up to the most recent surgical techniques. The risk of the manifestation of post-drug adverse effects influences any decision related to drug prescription and, finally, to their consumption. Some drugs are associated with a higher incidence of anomalies in children. For example, gingival hyperplasia induced by phenytoin is more frequent in children and adolescents than in adult persons. An overgrowth of the gingiva may be observed in more than 50% of the persons receiving phenytoin (Dilantin).

Keywords: epilepsy, gingival overgrowth, phenytoin.

INTRODUCTION

Epilepsy is defined as a chronic disease with various etiologies, characterized by the recurrence of some convulsive or non-convulsive critical manifestations, inducing an abnormal discharge of the cerebral neurons, whichever the clinical and paraclinical – the associated EEG ones included – signs. The treatment may reduce the frequency of convulsions or prevent them, in most of the cases, thus eliminating the crises such persons suffer along their life [1,2].

Incidence of epilepsy

Epilepsy is a chronic and invalidating pathology, affecting, according to WHO estimations issued in May 2015, approximately 50 million people all over the world, which defines it as one of the most frequent neurological diseases in all categories of age. In Europe, the incidence of epilepsy is estimated between 100 and 200 new cases/100,000 inhabitants, each year. In Romania, around 300,000-500,000 patients suffer with epilepsy; about 70% of these persons manifest only one type of crisis, the rest of them – two or three types. For example, children affected by myoclonic juvenile epilepsy may also have tonico-clonic crises and absence seizures, besides the myoclonic ones, which usually involve the upper members [3-5].

Epilepsy: Causes

The crises manifested before the age of 2 years are usually caused by high fever or by metabolic diseases, such as abnormal concentrations of blood glucose, calcium, magnesium, vitamin B6 or sodium. In cases of recurrent crises, they are probably caused by a hereditary cerebral diseases (e.g., nocturnal epilepsy of the frontal lobe, transmitted mainly autosomally). Many convulsive diseases, occurring for the first time between 2 and 14 years, have unknown causes, while those manifested after 25 years may be caused by cerebral structural lesions, as those produced by a cranial traumatism, a cerebral vascular accident or a tumour. However, in about half of the persons belonging to this group of age, the cause is unknown, so that the attacks are defined as idiopatic [6,7].

Epilepsy: Symptoms

Epileptic attacks appear as periodical disorders in the electrical activity of the brain, causing temporary cerebral dysfunctions. The symptoms vary as a function of the amplitude of the crisis,
being: partial (affecting only a cerebral area) or generalized (affecting extended cerebral zones, localized in both brain hemispheres) [8]. Partial crises may be simple (the person is fully conscious and perceives the surrounding medium) or complex (the state of conscience is altered, yet not fully lost). Partial crises may be partially simple, partially complex and partially continuous. Generalized crises cause the loss of consciousness and abnormal movements, usually beginning immediately. The loss of consciousness may be manifested for a short time or it may be prolonged. Generalized crises may be tonico-clonic, generalized primary epilepsy, absence seizures, atonic crises, myoclonic crises and epileptic status [9].

**Epilepsy: Treatment**

To reduce the risk of repeated crises, administration of anticonvulsive drugs may be necessary, mainly in patients who had more than one attack, with the exception of the cases in which the cause had been identified and fully solved. Anticonvulsive drugs may completely prevent the crises in more than half of the persons receiving them, while reducing significantly their frequency in one third of them. In spite of their efficiency, anticonvulsive drugs may have secondary effects, such as: anorexia, nausea, sickly feeling, epigastralgies, hirsutism and acne (in young women), allergic eruptions and, quite rarely, syndroms of colagenosis type, Stevens-Johnson, disseminated eritematosus lupus, colestatic icterus, hepatic necrosis, hyperglycemia, osteomalacia (caused by the deficit of vitamin D), hemorrhages in new-borns (deficit of vitamin K), leukopenia, agranulocytosis, trombocytopenia, aplastic or megaloblastic anemia (deficit of folic acid), limphadenopathy and hypertrophic gingivitis. Many of them cause sleepiness and sometimes – paradoxically – hyperactivity in children. Patients receiving anticonvulsive drugs should be informed on their possible secondary effects and discuss with the physician if manifestations of adverse reactions appear [10].

Phenytoin (Dilantin) is an anticonvulsive drug prescribed to epileptics, its secondary effect, manifested at the level of the oral cavity, being gingival overgrowth. The basic lesion, manifested as a slow, progressive, benign volumic growth of the gingival tissues, a secondary effect of the therapy with phenytoin, was described in 1939 by Kimbell, who reported that 57% of the 119 patients under investigation showed various degrees of gingival overgrowth, associated with the treatment with phenytoin, recommended against epileptic attacks [11]. Nowadays, 2 million persons receive this medication, overgrowths occurring in patients treated on long term, with a frequency varying between 0-95%, the most frequently reported values being of 40-50%. The first researches indicated an increase in the number of fibroblasts in patients treated with Dilantin, which also explains the term of hyperplasia, even if, today, the term of induced gingival overgrowth is preferred, as Hasell discovered that hyperplasia does not exist, neither collagen accumulations nor fibroblasts – abnormal as to their size or number – had been observed. Some authors report a direct and positive relation between the seric level of phenytoin and the salivary one, and the severity of gingival problems. Other authors found out no such correlation [12]. Generally, the existence of a relation between the phenytoin dose and gingivitis is acknowledged, and Adab and M.Vataman reported significant correlations between the level of gingival overgrowth and the level of the growth factor of fibroblasts in serum. No significant correlations were established with the age of the patient, daily or total phenytoin dose, duration of the therapy or the seric level of phenytoin [13,14].

Generally, the gingivitis induced by phenytoin is installed 2-3 weeks after the beginning of the therapy, attaining maximum values within 18-24 months. The initial clinical aspect is a painless volumic growth of the interproximal gingiva, affecting mainly the upper and lower frontal sectors, and more rarely of the lingual and posterior segments of the arch. In the beginning, the affected areas are isolated, then a generalized aspect appears. In cases in which infection and inflammation are not superposed one over another, the gingiva appears firm, coloured in pink, while bleeding is reduced (Fig.1).
Fig. 1. Slight gingival overgrowth in an epileptic child

As deformations are extending, delimitation becomes apparent on the median line of each tooth, after which deformations become coalescent towards the median line, false periodontal pockets are formed and the crowns of the frontal teeth get covered, the level of the gingival attachment remains constant, while the lesions may be either fibrous or they may show significant inflammatory compounds.

The hyperplasic tissues create an environment favoring the accumulation of bacterial plaque and of soft deposits, causing an inflammatory tissular reaction, producing pain, gingival bleeding, modifications in the position of teeth, as well as various degrees of periodontal problems (Fig. 2).

Fig. 2. Gingival overgrowth in a child treated with phenytoin [9]

Gingival hypertrophia is more frequently manifested in young patients with an unsuitable oral hygiene, subjected to treatments with phenytoin. Such hyperplasic proliferations may preserve their fibrous nature or they may acquire an inflammatory component in the presence of certain local irritative factors, which modifies the clinical picture as follows (Fig. 3):
- inflammation causes a volumic growth of the already hyperplasic tissues, along with the occurrence of gingival pockets;
- plaque retention increases in these false pockets, rendering more severe both inflammation and the hyperplasia;
- color of gingival mucosis becomes violet-red;
- possible hemorrhages and pain.

Fig. 3. Severe gingival overgrowth in a child treated with phenytoin [9]
Clinically, the following masticatory, physiognomic, phonetic modifications may be evidenced:

In cases of gingival overgrowths caused by antiepileptic medication, the therapeutical decision should be made only after estimating the extension of the hyperplasic tissues, its influence upon mastication, phonation and aesthetics, speech disorders, delayed eruptions, tissular traumatisms and secondary inflammation, which cause the periodontal disease. Most of the authors agree as to the relation between oral hygiene and induced gingivitis. Gingivitis may be reduced or even prevented by a careful oral hygiene and a professionally applied prophylaxy, the relation being extended towards the plaque index and the local irritative factors, the observation made being that this type of gingivitis does not appear in edentulous patients. Numerous studies demonstrated the possibility of preventing the occurrence of hyperplasic lesions through intense efforts, involving elimination of plaque and scale, even if, in some situations, in spite of such precautions, a volumic growth may appear, especially during the first seven months.

In patients with mild gingivitis forms, covering less than 1/3 of the crown, minute domestic and professional oral care for controlling bacterial growth are daily needed, namely careful brushings, irrigations, oral rinsings with 0.12% chlorhexidine. Initially, professional prophylactic measures and topic fluorization with tin fluoride are recommended for 4 consecutive weeks. Starting with the 5th week, evaluation of gingival condition, checking of the phenytoin levels – therapeutically occurring, under normal conditions, between 10-15 μg/ml - are preformed while, whether no improvements are observed, attempts are made at changing the anticonvulsive drug or at surgical removal of the hypertrophic gingiva.

In patients with severe gingivitis forms or in those who did not respond to the treatment, gingivectomy is necessary. As in any periodontal surgical intervention, supra- and subgingival scaling, a minute professional prophylaxy and root planning are performed, both prior to and after the operation as such, in order to prevent recidives, which may be immediate, within 3-4 weeks. Whichever the gravity of the hyperplasia, two types of possible treatments should be had in view: with drugs, surgical, or, sometimes, even combined.

Treatment with drugs assumes combat of the deficit of folic acid by a contribution of 15 mg/day intramuscularly up to the total disappearance of hyperplasia, followed by a treatment of 5 mg/ day, administered orally [12]. Another approach is based on the utilization as folates in solution, known as producing a significant inhibition of hyperplasia [9]. The authors explain this effect by the interference of phenytoin with the metabolism of the folic acid, showing that 37-90% of the subjects treated with anticonvulsive agents have folic acid deficiencies [9, 15, 16]. They assert that the subjects treated with phenytoin evidence a higher susceptibility of the gingival tissues to local inflammatory factors, which causes gingival overgrowth.

The surgical treatment means gingivectomia, as described by Glickmann (in 1974), accompanied by a rigorously-controlled hygienization. In certain cases, satisfactory results may appear within about 2 months from the last intervention while, within a year, the periodontium appears as stabilized. Some authors assert that numerous recurrences occurred after surgical interventions. The specific surgical approach in the hyperplasia induced by phenytoin includes classical gingivectomy, electrosurgery or intervention with internal flap. Utilization of the periodontal scalpel permits a rapid healing of the tissues, even if bleeding during and after the operation is intense, in such cases the cooperation from the part of the patient being essential.

The advantages of surgical laser include the absence of hemorrhage, sterilization in the operative field, lack of contact and autosterilization, a prompt healing and minimum postoperatory disconfort. Disadvantages refer to the high costs of the equipments, the need of hospitalization, the high level of the necessary medical expertise, the loss of the tactile feed-back, and additional protection for the eye. Surgery with periodontal flap assures a better healing, controls postoperatory bleeding and reduces postoperative pain. Selection of the surgical method, to be decided only by the specialist, is based on patient’s cooperation and compliance, extent of overgrowth and expertise of the surgeon [16].
References