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Antipsychotic Induced Hyperprolactinaemia: A New Risk Factor for Periodontal Disease

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Abstract

Aims: This case report aims to increase the awareness of the psychiatrist and dentist about the necessity of regular dental evaluation of the patients on antipsychotics, in order to reduce the incidence of periodontal disease.

Presentation of case: A 32 year old female patient suffering from schizophrenia, and on antipsychotic medications, since 11 years of age presented with complaint of pain and mobility in upper front teeth. Clinical and radiographic examination establishes severe generalised periodontitis associated with generalised gingival enlargement. Dexa test suggested reduced BMD; hormonal investigation implicates severe hyperprolactinaemia with no other hormonal abnormality. Periodontal management, withdrawal of Risperidone and dose reduction of Amisulpride, vitamin D, calcium supplements and Alendronate has been advised. Patient is on regular follow-up.

Discussion: Antipsychotics are the mainstay in the treatment of schizophrenia. Use of even atypical antipsychotics like Risperidone and Amisulpride has been associated with statistically significant decrease in the bone mineral density (BMD). Periodontitis is an inflammatory disease associated with progressive loss of alveolar lone resulting in tooth loss. There is greater propensity to lose alveolar bone, due to antipsychotic induced hyperprolactinaemia, in schizophrenia patients.

Conclusion: Regular monitoring of prolactin levels and dental screening programs are pre-requisite for patients on antipsychotics to prevent them from periodontal bone loss.

Keywords: Antipsychotics; Periodontitis; Schizophrenia

Introduction

Schizophrenia is a chronic mental disease characterized by delusions, hallucinations, disorganised speech or behaviour, and impaired cognitive ability [1].

Periodontitis is an inflammatory disease of the supporting tissues of the teeth caused by specific microorganisms resulting in progressive loss of alveolar bone. Bacterial lipo-polysccharides and other products act as systemic trigger that activates pro-inflammatory cytokines, interleukin -1 (IL-1), IL-6 and TNF-α which further induce secretion of acute phase proteins [2]. These inflammatory mediators though have a central role in periodontal tissue destruction are also evidenced to influence schizophrenic neurotransmitters [3, 4]. A case of antipsychotic induced hyper-prolactinaemia leading to osteoporosis and severe periodontal disease is reported. Regular monitoring of prolactin levels and dental screening programs, every three months of treatment is pre-requisite for patients on antipsychotics to reduce their adverse effects including periodontal bone loss.

Presentation of case

The female un-married patient aged 32 years reported to the Department of Periodontology, Hitkarini Dental College and Hospital, Jabalpur, M.P, India, with the complain of severe pain and sensitivity in upper front teeth since last 10 days. Pain was excruciating in nature which aggravated on eating of hot food and brushing but relieved on its own after some time. She also complained of bad breath since few months. Patient's medical history reveals that she is suffering from schizophrenia for 11 years of age and is on antipsychotics since then, in addition to a positive family history of schizophrenia and severe periodontitis.

On extra-oral examination, submandibular lymph nodes were slightly enlarged. On intra-oral examination oral hygiene status was fair (S-OHI) with generalized gingival enlargement. Grade II mobility was evident in Maxillary central incisors due to trauma from occlusion (Fremitus test positive, 2°) (Figure 1).

Patient had class I molar relation with an increased overbite (5 mm). Lips were incompetent with pathologic migration and Class III gingival recession evident in Maxillary and Mandibular anteriors (Figure 2). On probing, most of the periodontal sites exhibit bleeding and pus discharge corroborating with generalised deep periodontal pockets associated with significant mobility and furcation involvements. These clinical findings were well supported radiographically by orthopantomogram demonstrating significant loss of the bone support in both the arches.

Cognitive symptoms of the patient included disorganized speech, thought and attention which impaired the patient's social and vocational functioning. The patient gave the history of amenorrhoea for 5 years, though fertility and sexual dysfunction could not be commented upon. Assessment of Bone Mineral Density by Dexa test was significant. She is also having a postural hump, back pain and stunted growth which are often features of osteoporosis.

The patient is on SGA's (second generation Antipsychotics); Risperidone 3 mg since nearly 17 years and Amisulpride 100 mg-, 2 years. She also had Sertaline® 50 mg (SSRI-Selective Serotonin Reuptake Inhibitor) for 2years; Clonazepam® 10.5 mg- Benzodiazepine for 2 years; Prozen®- Chlorpromazine (FGA) 50 g. Calcium and iron supplement for 7 years.

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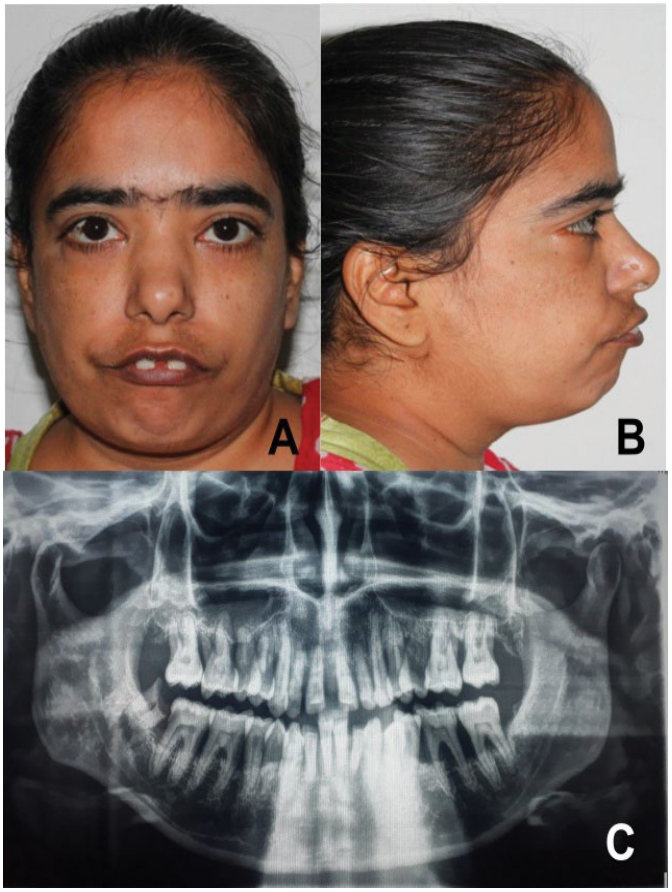

Figure 1: (**A**) Frontal view of the patient (**B**) Side view of patient (**C**) Ortho-pentogram showing generalized bone loss.

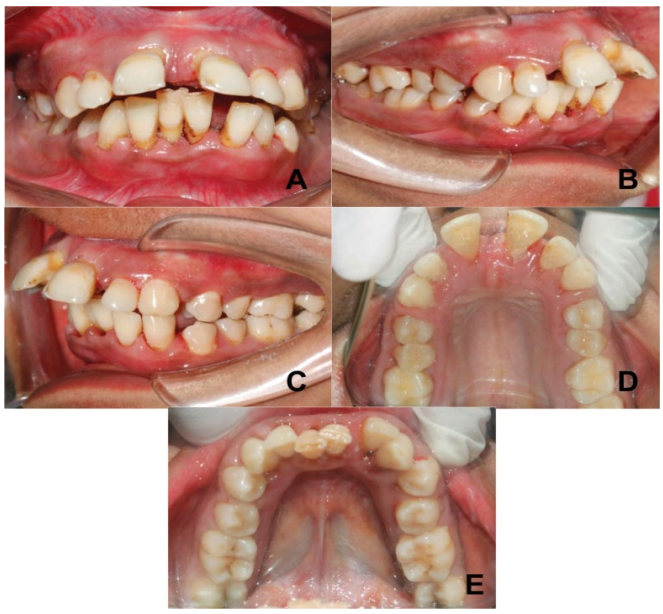

Figure 2: Intraoral photograph showing generalized inflammatory enlargement. (**A**) Proclined upper anterior teeth with midline diastema. (**B and C**) Right and left intra oral pictures respectively. (**D-E**) Maxillary and mandibular arch.

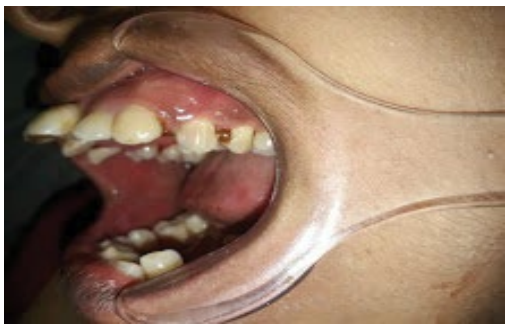

Figure 3: Local drug delivery by Periocol®-TC (Actisite) at the site of maxillary left premolar.

Discussion

Schizophrenia is the most common functional psychotic disorder, characterised by a disintegration of thought processes and emotional responsiveness [4]. Reports suggest that approximately 70% of the variation in the liability to develop schizophrenia is accounted for by genes, with the remaining 30% variation being explained by the environmental factors like physical inactivity, alcohol or smoking. Siblings of the proband have an 8.5% greater risk of developing this disorder as compared to the general population [5].

Individuals with the disorder can present the variety of manifestations, thus the symptoms are categorized as positive, negative, or cognitive [1]. The incidence of Schizophrenia is low (3-10,000), but the lifetime prevalence is approximately 1.1% of the population above 18 years of age with no sex predilection [4]. Moreover, schizophrenia patients are at a threefold risk of premature death and have shortened life expectancy of 10–20 years [6].

According to the American Psychiatric Association, second generation (atypical) antipsychotics (SGAs)—with the exception of Clozapine—are the agents of choice for first-line treatment of schizophrenia. SGAs are usually preferred over first generation (typical) antipsychotics (FGAs) because they are associated with fewer extrapyramidal symptoms. However, SGAs tend to have metabolic side effects, such as weight gain, hyperlipidemia, and diabetes mellitus [1].

All antipsychotics induce osteoporosis, the mechanism of which is complex, but the most possible one may be the hyper-prolactinemia [6]. Antipsychotic-induced hyper-prolactinemia in patients who are treated with first-generation antipsychotics and Risperidone is highly prevalent [7].

Some of the second-generation antipsychotics, such as Olanzapine, Quetiapine, Ziprasidone, Aripiprazole, and Clozapine, lack significant effects on prolactin [6].The extent of prolactin level increase shows great inter- and intraindividual variability [7]. However, when patients are treated with higher doses (doses of 4.2–5.2 mg daily) of Risperidone, women (65.6% of women of reproductive age) and younger patients (in 82–87% of patients) exhibit the greatest risk for hyper-prolactinemia; followed by Paliperidone and Amisulpride [7].

The routine prescription of two or more antipsychotics is not recommended because it increases the risk of drug interactions, non-adherence and medication errors [1]. As this patient was young women of reproductive age when she was first diagnosed with schizophrenia and was treated by simultaneous use of two atypical antipsychotics Risperidone and Amisulpride; the adverse effect of

hyper-prolactinemia; osteoporosis, besides periodontitis, had been bounteous. Patient reports symptoms of osteoporosis, specifically back ache since last 7 years (after approximately 14 years of continuous medication) which is gradually increasing in intensity. She, including her relatives never noticed any other symptom of hyper-prolactinemia or osteoporosis. As data suggests significant bone demineralisation occurs after approximately 8 years of antipsychotic medications; and hyperprolactinemia in patients taking long duration antipsychotic medications (mean duration: 22±7.8 years). However antipsychotic drugs are not listed under possible causes of osteoporosis by the World Health Organisation [8].

Patients taking SSRI drugs, particularly if used in combination with antipsychotic agents, may be at an increased risk for drug-induced hyper-prolactinemia [7]. This patient was having Risperidone with Sertaline; a SSRI for a period of two years.

Direct effect (short term) of hyper-prolactinemia is reported in up to 57% hyper- prolactinaemia women, it occurs on brain causing galactorrhoea. Indirect consequences include oligomenorrhoea or amenorrhoea, erratic or absent ovulation, sexual dysfunction, cardiovascular disease and reduced bone mineral density [7].

Antipsychotics-induced hyper-prolactinemia may influence bone metabolism in two ways. It directly affects bone turnover by stimulating bone resorption as, prolactin enhances production of mRNA for RANKL. On the other hand, it may cause hypogonadotropic hypogonadism. Prolactin levels, 2–4 times the upper limit, have significant adverse effects [7]; this patient reported a 20-25 fold increase in prolactin levels contributing towards low BMD and severe form of periodontitis. Apart from amenorrhea, this patient does not report any other sexual dysfunctions or related symptoms. Thyroid profile, luteinizing harmone, follicle stimulating harmone and oestrogen levels were normal. Of interest, estrogen levels in women do not always coincide with prolactin levels.

As reported, among schizophrenia patients treated with first generation antipsychotics or Risperidone, 23.2% of women have osteopenia (T score ≤ -1) [7]. Dexa test with a (T score ≤ -1) suggests osteopenic changes in this patient also. Due to prolactin-raising antipsychotics the relative risk of fracture at any site is increased upto 2.5-fold in premenopausal women with psychotic disorders [6].

Regulation of prolactin levels is complex, with estrogen causing increased production of prolactin and, serotonin (through 5-HT1A and 5-HT2 receptors) is stimulates its release. However, the major regulation is through Dopamine which acts at D2 receptors on lactotropes, to inhibit prolactin secretion. The prevalence of hyper-prolactinemia secondary to the use of an individual antipsychotic is roughly equated to the potency of its ability to block D2 receptors or the misfiring of dopaminergic neurons [7]. Dopamine dysregulation can be caused due to a number of factors including systemic infections and inflammations like periodontitis [4].

Advanced dental disease, especially periodontal bone loss is seen frequently in patients with schizophrenia. A bidirectional link, if any, between periodontal disease and schizophrenia has also been suggested. Schizophrenia impairs ability to plan and perform oral hygiene procedures. Some of the antipsychotic medications have adverse effects such as xerostomia or dry mouth [4].

Additionally, limited access to treatment because of lack of financial resources and adequate number of dentists comfortable in providing care further complicates.

Patients who have been suffering from schizophrenia for a longer period of time show greater periodontal destruction [9]. Additionally, Esfahanian et al, 2012 concluded in a review that there is greater propensity to loose alveolar bone in subjects with osteoporosis, especially in subjects with pre-existing periodontitis [10]. However, it also brings to the fore another aspect to this association, that schizophrenia is related to the activation of the inflammatory response system which plays a key role in periodontal destruction [11]. Schizophrenia is characterised by increased serum concentrations of IL-1R antagonist, IL-2, IL-6, positive acute phase proteins which are inflammatory mediator implicated in periodontal disease. These pro-inflammatory cytokines affect the neurotransmitters by enhancing Dopamine survival and inhibiting glutamate release leading to hypo-function of *N*-Methyl-D-Aspartate (NMDA) glutamate receptors which may lead to schizophrenia [4]. Elevated IL-6 levels have been also associated with duration of illness of schizophrenia [4]. In addition, increased prevalence of perio-pathogen, *P. gingivalis* and its correlation with severity of psychopathology of schizophrenia has been established [4].

Another consequence of antipsychotics induced hyperprolactinemia is sexual dysfunction in either sex [7]. Additionally, recent researches suggest an association between erectile dysfunction and chronic periodontitis in males, though any such association of sexual dysfunction like difficulties with libido or orgasm among females with periodontitis is not established [12]. However, this patient does not report any such symptoms.

In this patient, certain risk factors for osteoporosis could be modified; reduction in BMI, increase in physical activity, dietary calcium intake, vitamin D supplements, hormonal supplement for amenorrhoea [6]. Complete withdrawal of Risperidone and reduction in dosage of Amisulpride (200 mg twice daily) was done. Periodontal management included extraction of Maxillary central incisors, repeated SRP and curettage, plaque control, local drug delivery with Actisite® (2.0 mg tetracycline hydrochloride impregnated in collagen fibres) followed by maintenance phase. See Fig 3.

It is recommended that patients should be questioned on possible prolactin- related effects (menstrual disturbances in women, changes in libido or galactorrhoea in men and women, and erectile or ejaculatory dysfunction in men) until a stabilized dose is achieved and should undergo prolactin screening at initiation of 3 months of treatment. If levels are elevated, other etiological factors of hyper-prolactinaemia should be ruled out followed by dose reduction, switching drug or adding the prolactin sparing antipsychotic Aripiprazole. The addition of a D2 receptor agonist is another management option. The dopamine agonist Bromocriptine or Cabergoline, corrects hyper-prolactinaemia and increases BMD. Bromocriptine is associated with several adverse effects like postural hypotension, headache, dizziness and nasal congestion. Thus addition of Aripiprazole or switching to it reduced prolactin levels as well as side effects of Bromocriptine.

Combined oral contraceptives are indicated in women with symptoms of amenorrhea who are at risk of developing osteoporosis [7].

BMD monitoring is strongly recommended in all patients with schizophrenia and Bisphosphonates are advisable in patients at high risk for osteoporosis [7]. Additionally, dental evaluation should become an integral part of management of patients on antipsychotic medications.

Another aspect of management of patients on anti-psychotics is the incorporation of primary health care systems as in Project Leonardo.

Project Leonardo would be highly feasible in increasing patient health knowledge, self-management skills, and readiness to make changes in health behaviour. Physicians, care managers and patients, unanimous attempts would enhance patient management in this group of chronic illness [13].

Conclusion

Further controlled studies and adequate guidance are essential to increase awareness and understanding of the impact of antipsychotic-induced hyper-prolactinaemia on physical and periodontal health of schizophrenia patients. Long term interventional studies monitoring the cytokine profile, pre and post periodontal management followed by assessment of changes in the schizophrenia status of these patients needs to be undertaken.

Dental evaluations especially regular periodontal screening along with prolactin level and BMD monitoring should become an integral part of psychotic management. There is a definitive need to increase the awareness of the psychiatrist about regular dental evaluation of the patients so that no insult is added to the injury of this vulnerable group of patients. Additionally, dentist should also recognize specific treatment needs of dental patients on antipsychotics. Project Leonardo should be incorporated to fill the deficiency in health care system which can establish the link between patients on anti- psychoticsand their own illness.

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Competing interest

No competing interest

Consent

A written informed consent is taken from the patient's guardian for publication of this article

Authors contribution

Author 1: Dr Vandana D. Tripathi drafted the manuscript, revised it and made the final manuscript.

Author 2: Dr Kabbur. T. Chandarashekar guided the case

Author 3: Dr Sushama. R. Galgali guided the case

Author 4: Dr Rohit Mishra helped in treatment of case

Author 5: Dr Anushree Choudhary helped in maintaining the patient's compliance.

Author 6: Dr Honey Khatri managed the literature searches and treatment of patient

Author 7: Dr Ankita Deo managed the literature searches

Author 8: Dr Ashima Trivedi8 managed the literature searches

References

1. Patel KR, Cherian J, Gohil K, Atkinson D (2014) Schizophrenia: Overview and treatment options. P&T 39: 638-645.
2. Page RC (1991) The role of inflammatory mediators in pathogenesis of periodontal disease. J Periodontal Res 26: 230-242.
3. Ganguli R, Yang Z, Shurin G, Chengappa KN, Brar JS, et al. (1991) Serum interleukin-6 concentration in schizophrenia: Elevation associated with duration of illness. Psychiatry Res 51: 1-10.
4. Shetty S, Bose A (2014) Schizophrenia and periodontal disease: An oro-neural connection? A cross-sectional epidemiological Study. J Indian Soc Periodontol 18: 69-73.
5. Omoaregba HO, James BO, Eze GO (2009) Schizophrenia spectrum disorders in a Nigerian family: 4 case reports. Cases J 2: 14.
6. Wu H, Deng L, Zhao L, Zhao J, Li L, et al. (2013) Osteoporosis associated with antipsychotic treatment in schizophrenia. Int J Endocrinol pp: 1-7.
7. Bostwick JR, Guthrie SK, Ellingrod VL (2009) Antipsychotic-induced hyperprolactinemia. Pharmacotherapy 29: 64-73.
8. O'Keane V, Meaney AM (2005) Antipsychotic drugs: A new risk factor for osteoporosis in young women with Schizophrenia?. J Clin Psychopharmacol 25: 26-31.
9. Eltas A, Kartalci S¸ Eltas SD, Dundar S, Uslu MO (2013) An assessment of periodontal health in patients with schizophrenia and taking antipsychotic medication. Int J of Dent Hygiene 11: 78-83.
10. Esfahanian V, Shamami MS, Shamami MS (2012) Relationship between osteoporosis and periodontal disease: Review of the literature. J Dent 9: 256-264.
11. Gani Dk, Lakshmi D, Krishnan R, Emmadi P (2009) Evaluation of c-reactive protein and interleukin-6 in the peripheral blood of patients with chronic periodontitis. J Indian Soc Periodonto 13: 69-74.
12. Kalakondaa B, Koppolua P, Baroudia K, Mishra A (2016) Periodontal systemic connections-novel associations: A review of the evidence with implications for medical practitioners. Int J Health Sci 10: 293-307.
13. Ciccone MM, Aquilino A, Cortese F, Scicchitano P, Sassara M, et al. (2010) Vasc Health Risk Manag 6: 297-305.