The Interface between Psychiatry and Ophthalmology

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ABSTRACT

Objective: The aim of this article is to review the interface between psychiatry and ophthalmology at several levels, such as the influence of psychopharmacology on eye disorders, the occurrence of psychiatric symptoms in eye diseases, and the neuroophthalmological examination methods supporting the validity of psychiatric diagnoses.

Materials and Methods: We searched the PubMed computer database for the key words "Psychiatry" and "Ophthalmology" on the 28th of August, 2018 to obtain relevant articles which were consequently summarized.

Results: The results showed that most patients with ocular disease simultaneously have one or more psychiatric symptoms. We also found a prevalence of eye-related side effects in patients who use psychiatric drugs. At the same time, we observed that some ophthalmology methods of diagnostics can be used as diagnostic tools in psychiatry.

Conclusions: Most studies showed a significant relation between psychiatry and ophthalmology, such as eye symptoms and diseases following long-term use of psychotropics as well as psychiatric symptoms and syndromes in patients with eye disorders. Our review may be beneficial to psychiatrists, ophthalmologists, and, last but not least, the patients themselves.

KEYWORDS

depression; eye disease; psychopharmacology; dry eye syndrome; schizophrenia; blepharitis; bipolar disorder; pharmacotherapy

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INTRODUCTION

Mental disorders can be a manifestation of an organic brain disease – tumor, cyst, inflammatory process, traumatic encephalopathy, cerebral atherosclerosis, etc. The diagnostic of the cerebral process is important for a psychiatrist. Neuroophthalmological methods, with their results frequently reflecting brain pathology, include studies of acuity and field of vision, movements of the eyeballs, pupillary reactions, and the eye fundus. The results of neuroophthalmological diagnostics could potentially influence the psychiatric diagnosis and treatment strategy.

The aim of this article is to review the interface between psychiatry and ophthalmology at several levels, such as the influence of psychopharmacology on eye disorders, the occurrence of psychiatric symptoms in eye diseases, and the neuroophthalmological examination methods supporting the validity of a psychiatric diagnosis. This may be helpful for psychiatrists as well as ophthalmologists, from the clinical and scientific point of view.

MATERIALS AND METHODS

We searched the PubMed computer database for the key words "Psychiatry" and "Ophthalmology" on the 28th of August 2018 to get relevant articles. Afterwards, we summarized their content. We preferred large studies to individual case reports and recent findings to a historical knowledge. Only articles in English were considered for this review.

RESULTS

1. DEPRESSION AND ANXIETY IN OPHTHALMOLOGY

Chiang et al. (2013) conducted a retrospective follow-up observation to estimate the risk of depression and anxiety in patients with blepharitis using nationwide insurance data from 1997 to 2010 in Taiwan to identify annually patients with newly diagnosed blepharitis (N = 9764) and those without the disease (N = 39056). A chi-squared test was used to examine the distributions of baseline demographic characteristics and comorbidities between blepharitis and non-blepharitis patient groups. The results show that the incidence rate of anxiety and depression were (1.67-fold (95% CI = 1.46–1.70) and 1.29-fold (95% CI = 1.28–1.58) respectively) higher in the blepharitis cohort than in the non-blepharitis cohort. It was also higher in women than in men and increased with age in both cohorts (1).

Zhou et al. (2013) studied the prevalence of depression and anxiety symptoms in Chinese patients with glaucoma. The study included 506 patients with glaucoma. In the study the authors used the Hospital Anxiety and Depression Scale (HADS) and the Chinese-version of the Glaucoma Quality of Life-15 questionnaire (CHI-GQL-15). Multiple linear regression analyses were used to identifying the predictors of depression and anxiety. The results showed that in Chinese glaucoma patients the prevalence of depression and anxiety was 16.4% and 22.92%, respectively. The study also showed that independent predictors of anxiety were female gender (P = 0.001), younger age (P < 0.001), moderate and heavy economic burden (P = 0.009; P < 0.001 respectively), and the summary score of the CHI-GQL-15 (P < 0.001). The CHI-GQL-15 summary score (P < 0.001) and the duration of glaucoma (P = 0.019) were significant independent predictors of glaucoma. The authors concluded that, among Chinese patients with glaucoma, the prevalence of depression and anxiety was relatively high (2).

Chen et al. (2015) evaluated the risk of primary open-angle glaucoma (POAG) and primary angle-closure glaucoma (PACG) in depression patients with long-term use of selective serotonin reuptake inhibitors. The authors used data from the National Health Insurance Research Database in Taiwan and identified 26,186 patients with newly diagnosed depression and without preexisting glaucoma. The authors divided the patients into two cohorts. The first cohort included 13,093 patients with one year of serotonin reuptake inhibitors use. The second was a comparison cohort which included 13,093 patients who had never used serotonin reuptake inhibitors. All cohorts included patients > 20 years. The authors used the Kaplan-Meier method for evaluating the incidence of open-angle and angle-closed glaucoma between serotonin reuptake inhibitors and the comparison cohorts. For calculating the differences between the curves, the authors used a long-rank test. It was revealed that the incidence of open-angle and angle-closure glaucoma between the serotonin reuptake inhibitors and comparison cohorts had non-significant differences (long-rank test P = 0.52 for open-angle glaucoma, P = 0.32 for angle-closure glaucoma). Also, the authors concluded that the incidence of open-angle glaucoma in the serotonin reuptake inhibitors cohort was non-significantly higher than that in the comparison cohort (1.51 vs 1.39 per 1000 person-years), with an adjusted hazard ratio of 1.07 (95% CI = 0.82–1.40). The incidence of angle-closure glaucoma in the serotonin reuptake inhibitors was non-significantly lower than that in the comparison cohorts (0.95 vs 1.11 per 1000 person-years), with an adjusted hazard ratio of 0.85 (95% CI = 0.62–1.18). The authors concluded that the risk of primary open-angle and primary closed-angle glaucoma in the Chinese ethnic population in Taiwan does not depend on the long-term use of serotonin reuptake inhibitors (3).

The purpose of the Vaart et al. (2015) study from the University of North Carolina was to analyze the association between dry eye disease and depression and anxiety. The cases of anxiety (ICD-9 code 300, 300.00, 300.01, 300.02), depression (ICD-9 code 311, 296.2x, 296.3x), dry eye disease (ICD-9 code 375.15) and rheumatoid arthritis (ICD-9 code 714.0) were defined according to ICD-9 codes. The authors were interested in the associations between the diagnosis of dry eye disease and each of depression and anxiety. Because of it they separately estimated odds ratio between dry eye and each of the other disease. For estimating the associational ratio the authors used separate logistic regression models. A total of 460,611 patients were screened; 7,207 patients with dry eye were included, as were 20,004 patients with anxiety and 30,100 patients with depression. All patients were over the age of 18.

Separate odds ratios were calculated for dry eye disease, for anxiety, and for depression. The results show the estimated odds ratio between dry eye disease and anxiety was 2.8 (95% CI 2.6–3.0), while the ratio between dry eye disease and depression was 2.9 (95% CI 2.7–3.1). The study identified statistically significant associations between dry eye and the psychiatric diseases of depression and anxiety in a large population study (4).

In another study, to detect at which level of visual impairment psychological symptoms might appear, Palagyi et al. (2016) from Australia evaluated the prevalence and predicators of depressive symptoms in 329 older patients (aged ≥65 years) who were on a waiting list for cataract surgery. For measuring symptoms of depression, the authors used the 5-item Geriatric Depression Scale (GDS-5). Visual disability was assessed by the Catquest-9SF, visual acuity was measured binocularly and was corrected by the high contrast Early Treatment Diabetic Retinopathy Study (ETDRS) and binocular contrast sensitivity was measured by the Mars Letter Contrast Sensitivity Test. All measurements were done at least one month prior to surgery. Following a complete assessment, 94 patients (28.9%) were shown to have depressive symptoms. The depressive symptoms were significantly associated with visual disability (P = 0.020), higher comorbidity score (P = 0.020), and reduced quality of life (P = 0.003). The study demonstrated a high prevalence of depressive symptoms in older persons with cataract. The authors recommended creating an efficient referring system in order to reduce the surgery waiting time and to improve care coordination. This should include the screening and management of depressive signs during the surgery waiting time, which will play a great role in minimizing the negative psychological impacts of a cataract-related loss of vision in this group of patients (5).

Wan et al. (2016) from China assessed the association of depression and anxiety with dry eye disease by conducting a meta-analysis and systematic review that reported the incidence and prevalence of anxiety and depression in patients with dry eye disease versus healthy controls. The authors analyzed 22 studies consisting of 2,980,026 patients. The meta-analyses showed that dry eye disease was associated with an increased prevalence of anxiety (OR = 2.80, 95%, P < 0.00001) and depression (OR = 2.92, P < 0.00001). In patients with dry eye disease, the anxiety score (P = 0.007) and depression score (P < 0.00001) were significantly higher than in controls (6).

2. BIPOLAR DISORDER IN OPHTHALMOLOGY

Mehraban et al. (2016) from Iran measured peripapillary retinal nerve fiber layer thickness (RNFLT) in 30 patients with bipolar disorder and 30 age-matched healthy controls. The authors measured the mean RNFLT of the 4 quadrants by using Optical coherence tomography (OCT). The results showed that mean RNFLT was significantly less in the case group than in the controls, 99 ± 8 and 106 ± 8 μ, respectively (P = 0.001). The significant difference in RNFLT was in the superior (P = 0.040), inferior (P < 0.001), and nasal (P = 0.005) quadrants in both the case and control groups. The temporal quadrant was not reduced significantly compared to the control group (P = 0.907). The authors discovered that the duration of bipolar disorder had a variable significant relation with RNFLT. The authors concluded that measuring the reduction of the peripapilary retinal nerve fibre layer thickness in patients with bipolar disorder can be of beneficial value when studying neurodegenerative changes (7).

O'Bryan et al. (2015) evaluated the disturbances of visual motion perception in 61 patients with type I bipolar disorder (40 women, 21 men, mean age = 40) and 67 comparison subjects (35 women, 32 men, mean age = 39). The authors used psychophysical tests of contrast sensitivity, form discrimination, and dot motion discrimination for investigating visual perception in bipolar disorder. The results showed a deficit in dot motion trajectory discrimination in both euthymic and ill individuals with bipolar disorder (P = 0.007) and a nearly significant difference in global deficit in moving grating contrast sensitivity (P = 0.054). Patients with bipolar disorder were impaired in psychomotor processing but the result was not related to visual processing performance (8).

3. SCHIZOPHRENIA IN OPHTHALMOLOGY

The review by Gracitelli et al. (2015) showed that most studies on schizophrenia have focused on disturbances in higher-order brain functions associated with the frontal and pre-frontal cortex. However, recently there have been reported abnormalities in low-level sensory processes, such as the visual system. At early stages of the disease, patients report to have visual disturbances in perception. It is the variations in the dopamine and glutamate systems that have been highlighted in the pathophysiology of the disease. Also, the loss of retinal nerve fiber layer thickness has been well established in several neurologic diseases which also involve dopamine and glutamate dysregulation (9). Thirty schizophrenia patients and 30 age-matched controls were studied with spectral-domain optical coherence tomography and it was found that these measurements were reduced in schizophrenia patients. Cortical visual pathways have been described as magnocellular pathways, parvocellular pathways, and koniocellular pathways. Several studies have reported that visual impairment in schizophrenia patients could result from dysfunction in the magnocellular pathway. Tilt After Effects (TAE) in chronic schizophrenia patients were studied using neuroleptic drugs and compared with Parkinson's disease patients (9). It was shown that, if presenting peripheral fine gratings, schizophrenia patients produced results similar to those suffering from Parkinson's. It has been reported that schizophrenia patients make more color discrimination errors than control subjects. Studies concerning eye movements in schizophrenia patients have found reduced pursuit gain, low initial acceleration, and abnormal gain-corrective saccade interactions (9). Schizophrenia is associated with consistent deficits in visual processing in the early stage of the disease. It is therefore possible for ophthalmological assessment to be carried out as a further aid in the diagnosis of schizophrenia (9).

Ascaso et al. (2010) measured the retinal nerve fiber layer (RNFL) thickness by optical coherence tomography in

10 patients (males – 8, females – 2, mean age 39 +/– 13 years) with schizophrenia. The patients were from the Department of Psychiatry at the Hospital Clinico Universitario in Zaragoza, Spain. All patients had a corrected visual acuity of 20/20 (with a refractive error of +/– 2 spheric diopters) and intraocular pressure < than 18 mmHg. The group of patients was compared with ten age-matched controls. Peripapillary RNFL thickness, optic nerve head (ONH) measurements, macular thickness and volume were measured by optical coherence tomography (OCT) in both the patients and control group. The results showed a statistically significant reduction of the overall RNFL thickness in schizophrenic patients compared with controls (P = 0.047) and reduced peripapillary RNFL thickness in nasal quadrant in schizophrenic patients compared to controls (P = 0.048). No statistically significant differences were observed between schizophrenia patients and the control group with regard to ONH measurements and macular thickness and volume. The authors showed a statistically significant reduction of peripapillary RNFL thickness in schizophrenia patients evaluated by OCT (10).

4. SLEEP DISORDER IN OPHTHALMOLOGY

Ayaki et al. (2016) studied sleep and mood disorders in 715 Japanese patients with irritating ocular surface disease, 301 patients with dry eye disease, and 202 age matched healthy controls. Patients filled out the Pittsburgh Sleep Quality Index (PSQI) and the Hospital Anxiety and Depression Scale (HADS) questionnaires. Photophobia as the major symptom of dry eye disease was measured with two representative questionnaires (National Eye Institute Visual Function Questionnaire-25 and Morning/Eveningness questionnaires). The analyse showed that scores, respectively, for PSQI and HADS were 5.0 ± 3.3 and 8.9 ± 5.3 for allergic conjunctivitis (n = 78), 5.5 ± 3.1 and 9.5 ± 6.6 for chronic conjunctivitis (n = 124), 6.4 ± 3.2 and 11.1 ± 5.7 for severe dry eye disease (n = 146), and 5.5 ± 3.3 and 9.8 ± 4.0 for mild dry eye disease (n = 155). There was a significant difference among these diagnostic groups for PSQI (P < 0.05). The severity of dry eye disease significantly correlated with the PSQI and HADS (P < 0.05). The authors of the study demonstrated that sleep quality in patients with dry eye disease was significantly worse than in patients with other irritating ocular diseases, thus indicating a correlation with the severity of dry eye disease (11).

Liguori et al. (2016) performed an electrophysiological study of the visual system in patients with severe obstructive sleep apnea (OSA) in 6 women and 21 men (mean age 44 +/– 10) without medical comorbidities compared to a healthy control group (10 women, 17 men, mean age 41 +/– 11). The authors evaluated the integrity of the visual system by means of electroretinogram (ERG) and visual evoked potential (VEP). Day time sleepiness was assessed by using the Epworth Sleepiness Scale (ESS). The results showed a significant latency delay coupled with a significant amplitude reduction of P100 wave of VEP at all spatial frequencies in both eyes in patients with OSA compared to the control group (P < 0.001). No significant differences between patients with OSA and healthy controls were detected concerning ERG components. The authors also failed to find correlations between VEP and ERG components or polygraphic parameters and ESS scores in patients with OSA. The study showed that patients with OSA presented VEP alterations by a lower amplitude and longer latency of the P100 component than healthy controls. These altered electrophysiological findings may be the result of optic nerve dysfunction, which was provoked by airway obstruction, hypoxia, hypercarbia and acidosis, conditions frequently observed in patients with obstructive sleep apnoea (12).

5. PEDOPSYCHIATRY IN OPHTHALMOLOGY

Cumurcu et al. (2011) measured social phobia and other psychiatric problems in 42 children 8–13 years with strabismus and 47 healthy controls from Turkey. For evaluating social phobias, the authors used the Screen for Child Anxiety Related Emotional Disorders (SCARED). For each child, the researchers used the Children's Depression Inventory (CDI) and Schedule for Affective Disorders and Schizophrenia for School-Aged Children-Present and Lifetime Version (Kiddie-SADS-PL). The results showed that social phobia was diagnosed in 8 (19.04%) of the 42 patients with strabismus and in 1 (2.12%) of the healthy controls. Significantly higher were the CDI (P = 0.001) and SCARED (total score (P = 0.004), social phobia (P = 0.0001) and separation anxiety (P = 0.05) scores of strabismus patient than the control group. The authors concluded that there was a relationship between anxiety, depression, social phobia and children with strabismus, as evidenced by their data (13).

Karaman et al. (2016) in Turkey measured the effect of eye trauma on the mental health and quality of life in 20 patients aged 5 to 18 and their parents. For evaluating the quality of life for both parents and children, the authors used the Pediatric Scale of Quality of Life (PedsQL), and for evaluating mental health the Affect Disorders and Schizophrenia Interview Chart for school children, now and lifelong (AFSIC-NL), was used, along with the Child Post-Traumatic Stress Reaction Index (CPTSD-RI). 95% of patients were exposed to penetrating trauma and 1% to blunt. Nine patients were diagnosed with a mental disorder such as major depression (3.15%), posttraumatic stress disorder (3.15%), and generalized anxiety disorder (3.15%) according to AFSIC-NL. The authors found a statistically significant relationship between lens damage or initial visual acuity and the PedsQL-parent emotional functional scale. Also, the parents of patients had a mild posttraumatic stress disorder regarding the CPTSD-RI. The authors concluded that eye trauma can lead to the development of psychopathology in children (14).

Ikeda et al. (2013) evaluated the incidence of ophthalmologic disorders in 154 (79% male and 21% female) children with autism from the USA, all examined between 1998 and 2006. For analyzing the data, the authors used a SPSS statistical program. The subgroups of patients in the autistic spectrum were: 44.16% mild to moderate autism, 20.13% pervasive developmental disorder, 13.64% autism spectrum disorder, 11.04% severe autism, 7.14% moderate to severe autism, 3.25% Asperger's, 0.64% Rett syndrome. The findings showed that children with autism had as

follows: no ophthalmic problem (N = 61, p = 0.002), strabismus (N = 32, p = 0.001), amblyopia (N = 16, p = 0.127), refractive error (N = 44, p = 0.044). No relation was found with autism for children who had a history of prematurity gestation (<37 weeks). The findings suggest that ophthalmologic disorders were common in children with diagnoses in the autism spectrum (15).

Black et al. (2013) made a retrospective chart review of ocular abnormality in 44 patients (3:1 males to females, ages ranging 2 to 20 years) diagnosed with autism spectrum disorders (ASD) between January 2007 and October 2011 in the Greater Baltimore Medical Center (GBMC), USA. The results of the review showed that 52% (23) of patients with ASD at GBMC had some sort of ocular abnormality: strabismus 41% (18), significant refractive error 27% (12), anisometropia 7% (3), and amblyopia 11% (5). The authors found that the prevalence of amblyopia, anisometropia, and strabismus were higher among patients with ASD seen at the GBMC pediatric-ophthalmology practice than in the general population (16).

6. GERONTOPSYCHIATRY IN OPHTHALMOLOGY

Su et al. (2016) investigated the association between primary open-angle and primary angle-closure glaucoma with the risk of dementia in 6509 patients with glaucoma (3304 with open-angle and 3025 with angle-closure glaucoma) and a comparison cohort of 26,036 individuals without glaucoma and dementia in Taiwan. For evaluating the risk of dementia, univariate and multivariate Cox proportional hazard models were used. The research showed a higher risk of dementia in patients with glaucoma than in individuals without glaucoma (HR = 1.13, 95%, CI = 1.01–1.27). The patients with open-angle glaucoma had a 1.21-fold increased risk of dementia compared with the individuals without glaucoma (HR = 1.21, 95%, CI = 1.02–1.43). On the other hand, the patients with angle-closure glaucoma were not significantly associated with an increased risk of dementia compared with the healthy individuals (HR = 1.09, 95%, CI = 0.95–1.26). Patients aged ≥65 years with open-angle glaucoma were significantly associated with an increased risk of dementia compared to the healthy individuals (HR = 1.28, 95%, CI = 1.07–1.54). The authors concluded that patients with open-angle glaucoma were significantly associated with an increased risk of dementia compared with healthy individuals but not those with angle-closure glaucoma (17).

7. PSYCHOPHARMACOLOGY IN OPHTHALMOLOGY

A medical case report by Sears et al. (2015) suggested that long-term use of chlorpromazine can induce conjunctival secondary bilateral melanosis with unilateral limbal tumor (18). Chlorpromazine can also cause pigmentary or granular retinosis, benign natured pigmentary segregation on the lens or cornea as well as corneal edema (Sonmez and Aykan 2014) (19). Another case report by Karadaget al. (2015) indicated that the use of the antipsychotic drug aripiprazole can cause an acute transient bilateral myopia. However, the effect was reversed when patients replaced the drug (20). Similarly, Costagliola et al. (2008) suggested the use of SSRIs would increase intraocular pressure, induce optic nerve head changes, and predispose patients to angle closure, but this is dependent on each patient's individual tolerability of SSRIs (21). Additionally, SSRIs also affects the pupil diameter, aqueous humor dynamics, and optic nerve blood flow. In the review of Sonmez and Aykan (2014), a list of typical psychiatric drugs and their ocular side effects were described. These consist of thioridazine, butyrophenones, TCAs, benzodiazepines, mood stabilizers, lamotrigine, topiramate, and lithium. The side effects include retinitis pigmentosa, visual impairment, accommodation disorder, various eye movements disorder, nystagmus, and even oculogyric crisis (19).

The study of Borovik et al. (2009) refers to a case of a 55-year old female with a history of schizophrenia, depression, hypothyroidism, gastro-esophageal reflux and back pain. She was being treated with high dose of clozapine for 16 years and her cumulative dose was 4.67 kg, lithium carbonate 500 mg daily, thyroxine 100 µg daily and omeprazole 20 mg daily. She presented with bilateral pigmentary changes in her cornea and retina and stellate cataract. Clozapine is recommended in patients who experience pigmentary changes from chlorpromazine use, changes which are expected to resolve. The reason phenothiazine-related ocular changes happen is not known, but it is suspected to be related to photosensitization of tissues in which the drug has accumulated after sun exposure or that they alter the dopaminergic regulation of melatonin, which is suspected to increase the susceptibility of photoreceptors to damage by light. In this patient, it may be possible that these changes were produced by the high doses of clozapine, which also acts on dopamine receptors, since none of her other medications are known to have any such side effects (22).

The study of Emoto et al. (2011) was conducted to see whether psychotropic cessation in patients with drug-induced blepharospasm improves motor symptoms. Part or all of the patients´ psychotropic medication was withdrawn and their motor symptoms using the Jankovic rating scale were assessed. Twelve patients were sampled where psychotropics were administered before the onset of blepharospasm in all patients. The mean duration of treatment ranged between 3 and 120 months. At initial presentation, the Jankovic rating scale was 3 in eleven patients and 2 in one patient. After the cessation of medication, blepharospasm improved in all cases within 2 months. Therefore, it was concluded that blepharospasm was directly caused by the psychotropic agents (23).

Stein et al. (2015) measured the risk of open-angle glaucoma and bupropion use in 638,481 patients ≥35 years with no pre-existing open-angle glaucoma. For assessing the impact of bupropion and other antidepressant medications on the risk of open-angle glaucoma, the authors used the multivariable Cox regression modelling. The results showed that open-angle glaucoma developed in 15,292 patients (2.4%). Each additional month of bupropion use was associated with a 0.6% reduced risk of open-angle glaucoma (P = 0.007) after adjustment for use of other antidepressant medication. Patients with 24–48 months of bupropion use had a 21% reduced hazard (P = 0.0099) of open-angle glaucoma compared to non-users. The study

showed that the development of open-angle glaucoma was not significant associated with using selective serotonin reuptake inhibitors (P = 0.39) and tricyclic antidepressants (P = 0.95). The authors concluded that bupropion use may be beneficial in reducing the risk of open-angle glaucoma (24).

In a cross-sectional observational study by Acan et al. (2016), the authors aimed to determine the influence of selective serotonin reuptake inhibitors (SSRIs) on ocular surface and tear film stability. 36 patients (Group 1) and 36 healthy volunteers (Group 2) were enrolled (25). Group 1 was composed of patients in clinical remission of depression and/or anxiety to exclude the possible effect of the psychiatric disease on ocular disease when patients were using SSRIs. Other exclusions included subjects with other psychiatric or systemic disease, the usage of medication or contact lenses, pregnancy, lactation or ocular disease history for the past 12 months. Both Group 1 and 2 underwent detailed psychiatric and ophthalmological examination. The results showed no significant differences between the groups in terms of age and sex (P > 0.05) (25). The most commonly used SSRI among Group 1 was fluoxetine and the period of usage ranged between 2 and 120 months. It is not clearly seen whether the psychiatric disease or the medication used for its treatment were associated with the development of dry eye symptoms. Antidepressants could induce dry eye disease, as most of them inhibit amine (norepinephrine and serotonin) reuptake pumps, thus increasing functional amine-dependent synaptic transmission. In addition, serotonin receptors have been identified in the corneal and conjunctival epithelia, meaning that altered concentrations of serotonin by the use of SSRIs could affect the eyes (25).

Three cases of intraoperative floppy-iris syndrome (IFIS) were reported by Matsuo et al. (2016) during cataract surgery in patients using long-term antipsychotic drugs but without a history of selective α1 blockers (26). IFIS is a complication that may occur during cataract extraction in certain patients. This syndrome is characterized by a flaccid iris which billows in response to ordinary intraocular fluid currents, a propensity for this floppy iris to prolapse towards the area of cataract extraction during surgery, and progressive intraoperative pupil constriction despite standard procedures to prevent this (27). The first case refers to a 39-year old male with chronic angle-closure glaucoma who was being treated for schizophrenia with several classes of antipsychotic drugs, including haloperidol, chlorpromazine, aripiprazole, olanzapine, quetiapine, risperidone, and blonanserin for more than 7 years and topical β-blocker timolol for the glaucoma. In the second case, a 63-year old female was being treated for schizophrenia for more than 10 years with aripiprazole, quetiapine, and risperidone and the topical αβ-blocker levobunolol to treat glaucoma. In the last case, a 65-year old male had a history of haloperidol use for more than 10 years for an organic mental disorder and the topical β-blocker timolol for the treatment of glaucoma, as in case 1 (26). There are also 5 more cases reported in the literature with use of long-term chlorpromazine, risperidone, and quetiapine. All three cases presented with incomplete IFIS, no history of selective α1-blocker for glaucoma, and antipsychotic drug use. Even though antipsychotic drug related IFIS is not common, it seems that any class of antipsychotic drugs can cause such problems as they all have antagonistic effects on acetylcholine, histamine, and α-adrenergic receptors as side effects. Surgeons should take heed of this (26).

DISCUSSION AND CONCLUSION

An ophthalmological examination is part of the complex somatic and paraclinical examination of patients suffering from mental disorders. From previous articles, we can recognize the close relationship between psychiatry and ophthalmology. Unfortunately, only a small number of physicians examine their patients for side effects of psychotropic and ophthalmology drugs or level of anxiety before surgery. The possible value of ophthalmological symptoms and findings for a diagnosis and treatment of mental diseases is determined by the close anatomical and functional connection of the eye and the brain, by the commonality of their vascular system, and a high perceptibility of the eye to the side effects of psychotropic drugs. In an outpatient setting, neuroopthalmological examinations can be easily performed because they are usually cheap, quick, non-invasive, painless and widely available.

Most of the reviewed studies showed a significant relation between psychiatry and ophthalmology, such as eye symptoms in mentally ill subjects, mental problems accompanying eye diseases, and significant adverse side effects of psychotropics on the eye. Psychiatrists should be able to recognize signs and symptoms of eye disorders in people with mental problems, and ophthalmologists should be skilled enough to recognize symptoms of psychiatric disorders in their patients. An early recognition of symptoms in these two fields of medicine can help to start an adequate complex therapy and increase the quality of life of psychiatric as well as ophthalmological patients.

CONFLICT OF INTEREST STATEMENT

The authors declare they have no conflicts of interest.

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The Assessment of Serum Drug Levels to Diagnose Non-Adherence in Stable Chronic Heart Failure Patients

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ABSTRACT

Background: The aim of our study was to evaluate the prevalence of drug non-adherence in stable chronic heart failure (CHF) patients using serum drug levels (SDL) assessment.

Methods: CHF patients were prospectively enrolled during scheduled outpatient visit. Except standard procedures an unanticipated blood sampling for the SDL assessment was obtained. Analysis was focused on the prescribed heart failure and antihypertensive medication and was performed by liquid chromatography coupled with mass spectrometry. The patient was labelled as non-adherent if at least one of drugs assessed was not found in the serum. In the first half of patients multiple SDL have been evaluated during the follow-up.

Results: Eighty one patients were enrolled. The non-adherence was proven in twenty of them (25%). In the subgroup of thirty eight patients with multiple SDL evaluation the non-adherence raised significantly with increasing number of visits assessed together (21% for single visit, 29% for two of three visits assessed together and 34% for all three visits evaluated together, all $p < 0.001$).

Conclusion: The non-adherence was proven in significant part of stable CHF patients using SDL assessment. This method seems to be reliable and effective and should be a part of clinical assessment in selected patients with CHF.

KEYWORDS

chronic heart failure; drug non-adherence; pharmacotherapy; serum drug levels

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INTRODUCTION

Chronic heart failure (CHF) is a significant disease with increasing incidence and prevalence (1, 2). Life-saving pharmacological treatment based on Evidence based medicine remains the cornerstone of the care about CHF patients (2). Non-adherence to prescribed heart failure medication is common (3–10) and is related to higher hospitalisations and mortality rate (3, 5, 6, 8–10). To verify drug adherence may be clinically important in order to make decisions on proper treatment strategy in still symptomatic CHF patients.

However, to identify drug non-adherence may be challenging and none of the methods in use has been identified as optimal. In addition, the measurement itself is often biased by the effect of sensitizing patients and the results may be greatly affected (4). Indirect methods for drug adherence assessment include patients self-reporting (questionnaires), pill counting, and electronic medication monitoring and prescription refills (4). Monitoring systems have high specificity, but the sensitivity is reduced, because none of the methods is able to document the drug was actually ingested (11). The direct observation of drugs intake and the determination of serum or urine drug levels, using liquid chromatography coupled with mass spectrometry (LC-MS/MS) generally, are included in direct methods for drug adherence assessment (4). The reliability of direct drug measurement has been proven in studies assessing drug adherence in patients with apparent resistant hypertension (12–19). However, data in stable CHF patients are lacking.

OBJECTIVE

The aim of the study was to assess the drug non-adherence in stable CHF patients using the serum drug levels (SDL) monitoring.

METHODS

SUBJECTS AND DESIGN

We performed a prospective observational single centrum study. Consecutive CHF out-hospital patients followed on our clinic were enrolled. All participants were stable with set up CHF and antihypertensive medication. Both CHF patients with reduces and with preserved ejection fraction were suitable for the study. All patients were aged 18 years and older and gave written informed consent. The study was approved by the local Ethics committee and studies have been performed according to the Declaration of Helsinki.

The participants were enrolled to the study during scheduled outpatient visit (M1). Except standard procedures (physical examination, ECG, laboratory), an unanticipated blood sampling for the SDL measurement was performed. Analysis was focused primarily on the prescribed CHF and antihypertensive drugs, other medications were not systematically evaluated. Only drugs the patient confirmed as really intaken the evening before and the morning of the visit were considered.

According to the same rules, only in the first half of the consecutive patients multiple SDL have been evaluated during the follow-up (month 1 (at the time of enrolment, M1), month 3 (M3) and month 9 (M9).

THE DETERMINATION OF SERUM DRUG LEVELS

The determination of SDL was performed by LC-MS/MS (20, 21). The detection of the analysed substances was accomplished on a linear ion-trap mass spectrometer (LTQ XL, Thermo Scientific, San Jose, CA, USA) using electrospray ionization. All the procedures were performed as described before (12, 22).

Using this precise and sensitive technique we were able to measure nearly all the spectrum of CHF and antihypertensive medications (beta-blockers, angiotensin receptor blockers, calcium channel blockers, diuretics including mineralocorticoid receptor antagonists, alpha-blockers, centrally acting drugs, digoxin and amiodarone + active metabolite). However, we were not able to assess angiotensin-converting enzyme inhibitors due to analytical limitations. Fixed drug combinations (containing maximum two drugs in our study) were considered as each component taken separately for purpose of the analysis.

INTERPRETATION OF SERUM DRUG LEVELS RESULTS

Because the clinical interpretation of serum drug concentrations is difficult, any quantifiable amount of the evaluated drug was interpreted to mean that the drug was taken. Accordingly, only patient in whom the serum level of at least one drug was below the limit of detection was labelled as non-adherent. By applying this criterion for non-adherence, we eliminated uncertainties and ethical bias from the interpretation of low concentrations of drugs in the serum.

STATISTICAL ANALYSIS

Normal distributions of patients' data were evaluated with Kolmogorov-Smirnov test.

Numerical variables with a normal distribution were presented as mean ± standard deviation. Numerical variables with a skewed distribution were presented as median (interquartile range) and categorical variables were presented as percentage (%). Two groups comparisons of normally distributed variables were tested by unpaired t-test. The Fisher exact test was used for comparisons of non-normally distributed variables. For all tests p-value less than 0.05 was defined as statistically significant.

RESULTS

81 consecutive patients were prospectively enrolled. The principal characteristics of the study population are summarised in Table 1. The prescribed CHF and antihypertensive medications are shown in Table 2. For each patient enrolled, 4 (median) of 8 prescribed drugs were assessed.

Tab. 1 Principal characteristics of the study population.

Number of patients	81
women	*27 (33%)*
Age (years)	65 (58–71)
Left ventricular ejection fraction (%)	30 (25–41)
Systolic blood presure (mmHg)	130 (120–135)
Diastolic blood presure (mmHg)	75 (70–81)
Heart rate (beats per min)	71 (65–82)
Weight (kg) (mean ± SD)	93 ± 17
Body mass index	31 (27–34)
NT-proBNP (pg/ml)	702 (304–2212)
Diabetes mellitus	33 (41%)
Arteral hypertension	63 (78%)
Atrial fibrilation	11 (14%)
Etiology of CHF	
dilatated cardiomyopathy	*31 (39%)*
ischemic heart disease	*21 (26%)*
other cardiomyopathy	*6 (7%)*
significant valvular disease	*4 (5%)*
multifactorial	*14 (17%)*
unknown	*5 (6%)*

Unless stated otherwise, the data are expressed as median (25–75%).
Individual diagnosis are expressed as number of patients (% of study population).

Tab. 2 Prescribed CHF and antihypertensive medications.

BetaBlockers	71 (88%)
Angiotensin-converting enzyme inhibitors	48 (59%)
Angiotensin receptor blockers	14 (17%)
Furosemide	52 (64%)
Thiazides	52 (64%)
Aldosterone antagonists	57 (70%)
Calcium channel blockers	18 (23%)
AlphaBlockers	8 (10%)
Centrally acting drugs	2 (3%)
Ivabradine	3 (4%)
Amiodarone	23 (28%)
Digoxin	2 (3%)
Warfarin	30 (37%)
Statins	50 (62%)

Number of patients with prescribed individual drug/drug class (% of study population).

All of evaluated drugs were detected in the serum of 61 patients (75%) and the criteria for non-adherence were fulfilled in the remaining 20 patients (25%). One of all drugs was undetectable in 10 patients (12.5%), more than one in the serum of 9 patients (11%). None of the evaluated drugs was detectable in 1 patient (1.5%). The results of the adherence assessment are summarised in Table 3. The adherence and non-adherence according to individual drugs/drug classes are shown in Table 4 and Figure 1.

Tab. 3 Adherence assessment.

Number of patients	81
Number of prescribed drugs	8 (6–10)
Number of drugs evaluated	4 (3–4)
Number of adherent patients	61 (75%)
Number of non-adheretn patients	*20 (25%)*
one of all drugs undetectable	*10 (12.5%)*
more than one of all drugs undetectable	*9 (11%)*
none of all drugs indetectable	*1 (1.5%)*

Number of prescribed and evaluated drugs is expressed as median (25–75%).
Number of patients (% of study population).

Tab. 4 Non-adherence according to individual drugs/drug classes.

BetaBlockers	9% (6/71)
Angiotensin receptor blockers	14% (2/14)
Furosemide	10% (5/48)
Thiazides	12% (6/52)
Aldosterone antagonists	9% (5/57)
Calcium channel blockers	28% (5/18)
AlphaBlockers	13% (1/8)
Centrally acting drugs	0% (0/2)
Amiodarone	9% (2/23)
Digoxin	0% (0/2)

Non-adherence is expressed as percentage of patients with undetectable drug of total number of evaluated patients for individual drug/drug class the respective numbers (undetectable/total number) are in the brackets.
Furosemide was evaluated only if it was confirmed by patient as intaken in the morning.

Multiple SDL were planned to be assessed in the first 40 consecutive patients. However, two patients died during the course of the study therefore only data of 38 patients were analysed finally (Table 5). If each single visit (M1/3/9) assessed separately the non-adherence was proven in 21% of patients in this subgroup and was similar to the non- adherence of the whole study population (25%, p = 0.24). The non-adherence assessed for two of three visits together (M1+2, M1+3, M2+3, adherence defined as all drugs detectable in both blood-samplings) was proven in 29% and finally the non-adherence assessed for all three visits together (M1+3+9, adherence defined as all drugs detectable in all blood-samplings) was proven in 34% of

patients. With an increasing number of visits evaluated together the frequency of non-adherence has raised significantly (all $p < 0.001$).

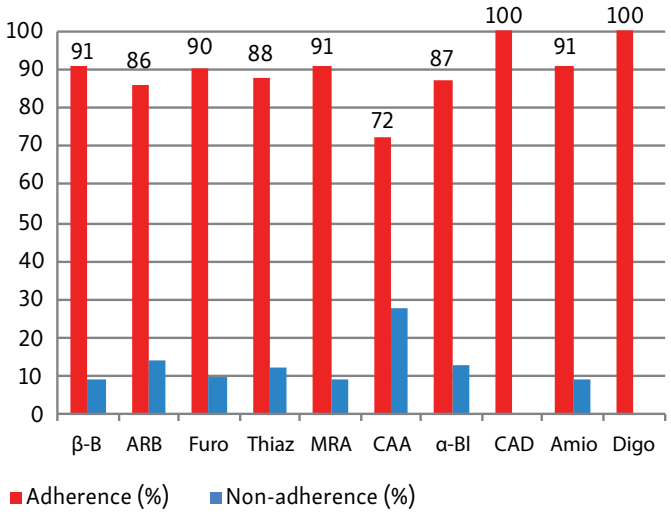

Fig. 1 Adherence/Non-adherence according to individual drugs/drug classes.
Abbreviations: β-B – BetaBlockers; ARB – Angiotensin receptor blockers; Furo – Furosemide; Thiaz – Thiazides; MRA – Aldosterone antagonists; CAA – Calcium channel blockers; α-Bl – AlphaBlockers; CAD – Centrally acting drugs; Amio – Amiodarone; Digo – Digoxin.

DISCUSSION

Non-adherence to prescribed medication has been reported in 11–60% CHF patients (3–10) as well as its negative effect on acute decompensations and mortality rate (3, 5, 6, 8–10). Finally, the negative economic impact of non-adherence to CHF medication has been also proven (23, 24).

However, to recognise drug non-adherence may be challenging in daily clinical practice. In CHF patients the adherence has been evaluated on the basis of pharmacy and insurance records analysis (prescription refills) or on patients self-reporting (questionnaires) in the previous studies (3–10, 23, 24). Unfortunately, the sensitivity of self-reporting is reduced (4), which has been documented in retrospective study with apparent drug resistant arterial hypertension patients. Only nearly half of non-adherent patients was identified using one of the most frequently used questionnaire The Morisky Medication Adherence Scale (MMAS-8) compared to SDL evaluated by LC-MS/MS (19). On the other hand, prescription refills is a method much more suitable for research purpose than for clinical evaluation (4, 25). The suitability and the reliability of direct drug monitoring have been demonstrated in several studies with patients who presented with difficult-to-control arterial hypertension. Using drug monitoring in the serum (12–15, 18, 19) or in the urine (16, 17) the non-adherence has been reported in 25–86% of these patients.

Moreover, the British and Czech authors have shown that screening for non-adherence using LC-MS/MS and subsequent results discussion with the non-adherent hypertensive patients led to improved drug adherence and significant blood pressure drop (26). In addition, a recent study has demonstrated this approach as cost-saving strategy in patients with apparent resistant hypertension (27).

Based on the above listed data, drug monitoring can be considered as suitable method for drug adherence assessing in patients with apparent resistant arterial hypertension. However, to the best of our knowledge, the use of this method in stable CHF patients has not been reported before. We have only proved the non-adherence in significant part (44%) of patients presenting with acute decompensated heart failure using SDL monitoring in our previous study (22).

In the present study we have identified the non-adherence in 20 of 81 (25%) CHF patients. Compared to previous studies (5, 6, 8, 9), the frequency of non-adherence was relatively low and the adherence to individual drug classes including diuretics and beta-blockers was relatively high in our study. We can only speculate about reasons. It could be explained by the fact that only stable patients in long-term follow-up with gradually titrated medication were enrolled to the study. By this way some of known unfavourable influences, such as drug related site effects or doctor-patient relationship related factors could be eliminated.

It is obvious that a single SDL assessment provides information about actual adherence only and it does not have to correspond to long-term cooperation. This idea is in line with our results. In subgroup of the first 38 consecutive patients multiple SDL evaluations have been performed (month 1, 3 and 9) and the frequency of non-adherence has risen significantly with an increasing number of visits evaluated together. Assessing single visit, the non-adherence was proven in 21% of patients, for two visits together in 29% and for all three visits in 34% of patients (all $p < 0.001$). Unfortunately, even multiple SDL monitoring cannot rule out "white-coat adherence" thought those patients, who took their medication only before scheduled visits.

The qualitative assessment of SDL could be another reason for possible drug non-adherence omission in our study (4). Any detectable amount of drug was interpreted as a proof of adherence, therefore it was not able to identify patients taking the medication irregularly or in

Tab. 5 Non-adherence in subgroup with multiple SDL evaluations.

Number of controls evaluated together	Non-adherence
Single control (median)	8/38 (21%)
M1	*8/38 (21%)*
M3	*7/38 (18%)*
M9	*8/38 (21%)*
Two controls (median)	11/38 (29%)
M1+3	*11/38 (29%)*
M1+9	*12/38 (32%)*
M3+9	*10/38 (26%)*
Three controls (M1+3+9)	13/38 (34%)

Numbers of non-adherent patients/total number of patient in subgroup (% in the brackets).

lower doses (4). However, the quantitative evaluation of drug levels is difficult in daily clinical practice. Serum and urine concentrations may vary widely between-individual and within-individual due to fluctuations in drugs pharmacokinetics, genetic polymorphisms (cytochromes P450, drug transporters etc.), disease-induced poor absorption, and renal elimination or drug-drug interactions (4). In addition, it is generally impossible to ensure suitable time interval between drug intake and unanticipated blood sampling during the out-hospital visits. The combination of drug monitoring and pharmacokinetic simulations seem to be a possible solution of this problem (4, 18), unfortunately probably too complicated for daily clinical practise.

Another limitation of our study was the exclusion of angiotensin converting enzyme inhibitors from the analysis. Evaluation of active metabolites is necessary for reliable assessment of this drug class, which was not available in our hospital at the time the study was performed.

The extension of drug monitoring for adherence assessment may be limited by its cost and technical requirements. But, the drug non-adherence identification may have important clinical consequences in still symptomatic patients with set up medication who are generally candidates for other expensive therapeutic options (resynchronization, mechanical circulatory support, heart transplantation). Non-adherence evidence should lead to close physician-patients cooperation with maximal effort to improve the adherence instead of extension of other therapy first of all. As well as in apparent resistant hypertonic patients (27), we can suppose this approach to be cost-effective in CHF patients. But this assumption has to be confirmed by further studies.

CONCLUSION

Based on serum drug levels monitoring, non-adherence was proven in significant part of stable chronic heart failure patients. We believe this method is reliable and effective in drug adherence evaluation and should be a part of clinical assessment in still symptomatic patients with chronic heart failure, particularly before searching for new therapeutic options.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Calcemia and Inflammatory Markers in Early-Onset Neonatal Infection

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ABSTRACT

Introduction: Ionised hypocalcemia (S-Ca^{2+}) has been repeatedly observed in neonates with sepsis. Our aim was to evaluate total calcemia (S-Ca) and its relationship to laboratory markers of infection.

Methods: We retrospectively evaluated total calcemia (S-Ca) and its relationship to laboratory markers of sepsis/infection (serum levels of C-reactive protein – S-CRP and procalcitonin – S-PCT) in 29 full-term neonates with early-onset neonatal infection hospitalized at our neonatology ward between 2012 and 2016. The control group consisted of 705 neonates without infection.

Results: In neonates with early-onset infection , the S-Ca on day 1, 2 and 3 was significantly lower ($p < 0.0001$; $p < 0.0001$; $p = 0.05$ versus controls) same as the pooled S-Ca ($p < 0.0001$ versus controls). There was a weak negative correlation between pooled S-Ca and S-PCT, or pooled S-Ca and S-CRP ($r = -0.22$, $p = 0.06$; $r = -0.19$, $p = 0.09$).

Conclusion: S-Ca was decreased in neonates with early-onset infection and did show a slight tendency to inverse correlation with S-CRP and S-PCT. Pediatricians must be aware of the fact that a drop in total S-Ca should alert their attention to the risk of neonatal infection, and, likewise, that the children with neonatal infection are at a higher risk of hypocalcemia with all its consequences.

KEYWORDS

calcium; early-onset neonatal infection; neonate

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INTRODUCTION

Neonatal hypocalcemia can occur in premature or hypotrophic children, other risk factors include infection, maternal diabetes, perinatal asphyxia, low calcium intake, maternal hyperparathyroidism, phosphate overload, transient or primary hypoparathyroidism, hypomagnesemia, hepatopathy or end organ resistance to the biological actions of parathyroid hormone (PTH) (1–7). Hypocalcemia, in particular low level of serum ionized calcium (S-Ca^{2+}), has been repeatedly reported in neonates with sepsis (1–7).

Newborns with hypocalcemia are either asymptomatic, or may present with hypotonia, apnea, poor feeding, jitteriness, seizures, cardiac failure. Signs of hypocalcemia rarely occur unless S-Ca drops below 1.75 mmol/l (7).

The pathogenesis of hypocalcemia in sepsis is explained by the increased secretion of procalcitonin, the precursor of calcitonin, with consequent hypocalcemic effects (8, 9).

The upregulation of calcium-sensing receptor (CaSR) by cytokines, in particular tumor-necrosis factor alpha (TNF-alpha), interleukin-1 beta (IL-1beta) and IL-6 may also play a significant role in the pathogenesis of hypocalcemia in sepsis. The upregulation of CaSR results in decreased serum PTH and 1,25-dihydroxyvitamin D and calcium levels (10–11).

Administration of aminoglycosides, in particular gentamicin, to neonates, is also associated with a drop in calcemia (12–13). This could be explained by the fact that aminoglycoside antibiotics are CaSR agonists (14–15).

Ionised hypocalcemia is considered a negative prognostic factor in the neonatal sepsis, together with calcitoninemia and serum levels of PTH (5, 6, 8). Furthermore, ionised hypocalcemia is associated with organ dysfunction in children admitted to intensive care unit (4).

Our aim was to retrospectively evaluate total calcemia (S-Ca) and its relationship to laboratory markers of sepsis/infection (serum levels of C-reactive protein – S-CRP and procalcitonin – S-PCT) in neonates.

PATIENTS, MATERIALS, METHODS

Between the years 2012 and 2016, 3441 neonates were hospitalized at our neonatology ward. Total calcemia was assessed in 988 samples drawn from 828 babies. Out of those, neonatal infection was diagnosed in 29 full-term children (Table 1), based on Töllner scores (abnormal skin color, prolonged capillary refill time, muscular hypotonia, bradycardia, apnea, respiratory distress, hepatomegaly, gastrointestinal symptoms, number of leukocytes, increased number of immature neutrophils, thrombocytopenia, metabolic acidosis) >5 points (16) and S-CRP or S-PCT elevation. All 29 children were treated by intravenously administered gentamicin and ampicillin for seven days, with a favorable outcome. The control assessments of inflammatory markers and S-Ca were based on the clinical situation of the patients The blood samples were collected on days 1, 2 and 3 of the infection, however all three parameters (S-Ca, CRP, PCT) were not always assessed in each obtained sample (vide infra).

Tab. 1 Patient data.

Total number of patients	**29**
Boys : girls ratio	16 : 13
Mean and median gestational age ± SD (weeks)	39.4; 39.5 ± 1.9
Mean and median birthweight ± SD (grams)	3310; 3355 ± 537
Mean and median body length ± SD (cm)	50; 50 ± 2.5
Mean and median age at onset of infection ± SD (days)	1.6; 1.0 ± 1.4
Number of blood draws in children with early-onset infection within the first three days of illness	87
Mean and median age at the time of blood draws ± SD (days)	1.8; 2.0 ± 0.9
Control group – total number	705
Boys : girls ratio	413 : 292
Total number of blood draws in control group	800
Mean and median age at the time of blood draws ± SD (days)	2.2; 2.0 ± 1.8

SD: standard deviation

Total calcemia (kit CalciumC – Abbott, method Arsenazo III; analyser Architect) was assessed on day 1 of the infection in 29 patients (n = 29; 100%); on day 2 (n = 14; 48.3%) and on day 3 (n = 17; 58.6%).

C-reactive protein (kit CRP Vario, method turbidimetry/imunoturbidimetry; analyser Architect) was assessed on day 1 of the infection (n = 29; 100%), on day 2 (n = 27; 93.1%) and on day 3 (n = 24; 82.8%).

Procalcitonin (kit Liaison Brahms PCT II GEN, chemiluminiscence analysis CLIA, analyser Liaison XL) was assessed on day 1 of the infection (n = 19; 65.5%), on day 2 (n = 21; 72.4%) and on day 3 (n = 15; 51.7%).

As mentioned above, out of 828 neonates, where S-Ca was assessed, 29 were diagnosed with early-onset infection. Therefore, 799 neonates (424 boys and 375 girls) were considered as free of infection/sepsis. Due to the fact, that all 29 patients suffered from early-onset infection within the first three days of life and we evaluated their biochemical data (S-Ca, CRP, PCT) in the following three days, the age-matched control group was selected to include S-Ca results from full-term neonates under 6 days of age (n = 705; 413 boys and 292 girls) (Table 1). The reasons for blood draws and biochemical assessments (including S-Ca) in these children were: hypotonia, tachypnea, jaundice, body temperature changes, vomiting, maternal risk factors (diabetes, hypertension, nicotinism/drug addiction). None of the controls presented with infection or severe metabolic disorder.

Unpaired t-test and Pearson's correlation were used for statistical analysis (SigmaPlot software). The values were expressed as mean and median ± standard deviation (SD).

RESULTS

The mean value of S-Ca in 799 children without infection was 2.36 ± 0.19 mmol/l. The mean value of S-Ca in 705 children (considered as a control group) was 2.38

Tab. 2 Correlations between S-Ca and S-CRP and S-PCT, respectively.

Parameter	S-CRP day 1	S-CRP day 2	S-CRP day 3	S-PCT day 1	S-PCT day 2	S-PCT day 3
S-Ca day 1	-0.07	-0.1	-0.1	-0.08	-0.09	-0.1
S-Ca day 2	-0.08	-0.1	-0.08	-0.08	-0.1	-0.09
S-Ca day 3	-0.1	0.03	-0.08	-0.09	-0.08	-0.09

± 0.21 mmol/l. In neonates with infection , the mean value of S-Ca on day 1 was 2.16 ± 0.30 mmol/l, median 2.13 mmol/l; 2.12 ± 0.18 mmol/l, median 2.03 mmol/l on day 2 ($p < 0.0001$ versus controls; unpaired t-test) and 2.27 ± 0.18 mmol/l, median 2.32 mmol/l on day 3 ($p = 0.05$ versus controls; unpaired t-test). The mean value of the pooled S-Ca in neonates with infection was 2.18 ± 0.24 mmol/l, median 2.19 mmol/l ($p < 0.0001$ versus controls; unpaired t-test).

The mean values of S-CRP were 24.63 ± 29.58 mg/l, 34.63 ± 31.46 mg/l, and 22.02 ± 18.64 mg/l (normal < 5 mg/l) on days 1, 2 and 3, respectively. The median values of S-CRP were 12.55 mmol/l, 23.65 mmol/l and 19.25 mmol/l on days 1, 2 and 3, respectively. The mean value of the pooled S-CRP in neonates with sepsis was 27.16 ± 27.73 mg/l; median 19.0 mg/l.

The mean values of S-PCT were 20.85 ± 23.30 µg/l, 23.44 ± 36.12 µg/l and 8.05 ± 16.71 µg/l (normal < 0.5 µg/l) on days 1, 2 and 3, respectively. The median values of S-PCT were 7.12 µg/l, 6.0 µg/l and 2.77 µg/l on days 1, 2 and 3, respectively. The mean value of the pooled S-PCT in neonates with sepsis was 18.35 ± 27.64 µg/l; median 6.0 µg/l.

There were no mutual correlations between S-Ca and S-CRP or S-PCT on days 1, 2 and 3. (Table 2).

We found weak inverse correlations with tendency to statistical significance between S-Ca and S-PCT ($r = -0.22$; $p = 0.06$), and S-Ca and S-CRP ($r = -0.19$; $p = 0.09$), respectively, once the data were pooled.

DISCUSSION

Our paper gives evidence about a transient drop in total serum calcium in the course of early-onset neonatal infection. Furthermore, we also found a tendency to slight inverse relationship between pooled total serum calcium levels and biochemical markers of inflammation (CRP and PCT), with tendency to statistical significance.

Regarding our patients, the relationship between S-PCT and S-Ca, in particular the hypocalcemic effect of PCT, was also considered (8, 9, 17). The relationship between PCT and serum levels of calcium remains unclear and rather controversial, as there is no evidence of PCT binding to the calcitonin cellular receptors (18). In a study with healthy volunteers, infusion of calcium gluconate physiologically stimulated the release of mature calcitonin with only minimal effects on the S-PCT levels (19). Furthermore, septic patients with ionised hypocalcemia were reported as having low serum 25(OH)vitamin D levels which were inversely correlated with S-PCT (20). In another study in patients with septic shock, S-PCT levels were correlated with the severity of disease and S-CRP, but not with $S\text{-}Ca^{2+}$ levels (21). In adult patients with sepsis, the low $S\text{-}Ca^{2+}$ concentrations were inversely related to S-PCT, TNF-alpha and IL-6 (17). Therefore, in patients with sepsis/infection, the combined hypocalcemic effect of PCT together with TNF-alpha, IL-1, IL-6, and aminoglycoside up-regulation of CaSR can not be ruled out (10–15, 17).

All our patients with early-onset neonatal infection received appropriate antibiotic treatment and the clinical course and outcome was favorable. None developed organ dysfunction. The S-Ca was not found to be a predictor of further changes in markers of inflammation, as there were no mutual correlations between S-Ca and S-CRP or S-PCT on days 1, 2 and 3, respectively (Table 2).

We are well aware of the limitations of our paper as $S\text{-}Ca^{2+}$, albumin-adjusted-Ca, serum levels of 25-OH-vitamin D, S-PTH, TNF-alpha, IL-1 and IL-6 were not assessed, together with the fact that all three observed parameters (S-Ca, CRP, PCT) were not always measured in each obtained sample in the course of infection. Furthermore, we analysed only full-term neonates with early-onset infection and our results are probably not fully applicable to pre-term neonates.

In conclusion, total S-Ca was decreased in neonates with early-onset infection and did not show any strong or significant correlation with S-CRP and S-PCT, however, there was a tendency to inverse relationship with these parameters once the data were pooled. Pediatricians should be aware of the fact that low total S-Ca should alert their attention to the risk of neonatal infection/sepsis, and, likewise, that the children with neonatal infection/sepsis are at a higher risk of hypocalcemia with all its consequences.

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Dependence of Deciduous Tooth Eruption Terms and Tooth Growth Rate on the Weight-Height Index at Birth in Macrosomic Children over the First Year of Life

Olga Garmash*

ABSTRACT

The aim of this research is to study the effect of body overweight at birth (fetal macrosomia) on the processes of tooth eruption and tooth growth during the first year of life in children in the Kharkiv City (Ukraine) population. One of the research tasks is to examine the features of deciduous teeth eruption in children who were born with macrosomia with different values of the weight-height index at birth.
Materials and methods. The medical records of the children born between 1977 and 2013 have been analyzed. The database has been collected in one of the Kharkiv City clinic. The Main Group is comprised of the medical records of the children (separately for boys and girls) born with fetal macrosomia. All the medical records of the Main Group have been divided into subgroups taking into account the gender and the harmonious (well-balanced) development coefficient. The Comparison Group is comprised of the medical records of the children also born within the normal term range, but with weight and height that correspond to the gestation age (fetal normosomia).
To determine the average time of the first tooth eruption, as well as the deciduous teeth growth rate for each of the groups under the study, we have used the hypothesis about a linear dependence between the number of erupted teeth and the age of the child. The statistical data processing and verification of the consistency of this hypothesis is performed using the multiple linear regression analysis with the STATISTICA 6.0 software package (Multiple Regression module). The number of delayed eruption and premature eruption cases observed is calculated along with the corresponding confidence intervals for the significance level, p, of less than 0.05, taking into account the binomial distribution of the random variable.
The results of the study indicate a slowed growth rate of deciduous teeth in children born with macrosomia, as well as an increased number of cases (by a factor of 2 to 4 times) of deviations in the timing of teeth eruption compared to regional norms. The smallest growth rate of deciduous teeth and the smallest number of teeth at the age of one year are registered in macrosomic boys and macrosomic girls with a long body and a relatively reduced birth weight, as well as in macrosomic girls with intrauterine obesity. The macrosomic girls with intrauterine acceleration with obesity at the background have the largest average tooth growth rate and the largest percentage of premature eruption cases among all subgroups.
Conclusions. The somatometric features of fetal macrosomia suggest the influence on the number of teeth that erupt by a certain age. The data on the deviation from the generally accepted terms of teeth eruption in children born with macrosomia, can be the basis for developing new and improving existing prevention programs aimed at preserving dental health.

KEYWORDS

fetal macrosomia; height-weight index; deciduous teeth

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INTRODUCTION

The preventive care issues aimed at reducing the caries intensity and eliminating other dental disorders in children can not be solved without understanding the mechanisms for deciduous teeth eruption and their maturation. The patterns of both deciduous and permanent teeth eruption pertains to children's general-somatic health. These patterns are also components of somatic health. The processes of coronal and root teeth system formation and mineralization, and the tissues surrounding them, begin to develope long before the child's birth and are the stages of craniofacial complex development (1).

A great number of hereditary and environmental factors affect the terms, parity and the sequence of tooth eruption (2). The influence of prenatal period, preterm birth, state of health and parents' age has already been proved (3). Several studies have been recently carried out to reveal the effects of the pathological course of pregnancy on dental health (4).

The processes of teeth eruption and maturation are influenced by childhood diseases and feeding preferences (5, 6). There are sexual, racial and even regional differences in the mean values of teeth eruption terms (7). The influence of weight gaining rate in the first months of life on the processes of deciduous teeth eruption is also studied (8).

In the previous research (9), we have revealed a significant impact of weight-growth parameters at birth on the terms of teeth eruption in children in the Kharkiv City. The results obtained agree with the studies of other scientists (10), and prove that fetal macrosomia leed to the violation of maxillofacial system development (11). Diagnosis of fetal macrosomia is made when the weight of the child's body at birth is equal to or more than 4,000 g (12). Using the chronological standards (1) for the desidious teeth eruption, it is found that macrosomic newborns have, on average, a lower teeth growth rate and a larger spread in the number of teeth that have erupted before a certain age. Moreover, the effect of weight gaining rate after birth on these processes is excluded (11).

Different researchers give controversial information about the terms of teeth eruption in macrosomic newborns (1, 13, 14). Some authors (14) indicate the premature eruption of deciduous teeth in macrosomic newborns, whereas Khuraseva (13), on the contrary, reveales a delay in the deciduous teeth eruption in this group of children. Existing controversies can be explained by many factors. The literature shows that many factors can lead to the macrosomic child birth. The processes that cause intrauterine weight gainining may also affect the terms of teeth eruption. As is well known, macrosomic children do not comprise a homogeneous group due to various factors leading to the formation of fetal macrosomia and the individual characteristics of newborn infants.

One of the classifications of fetal macrosomia is grounded on the harmonious development coefficient, which has been introduced and later repeatedly improved by Kharkiv scientists (15). This classification is based on the weight-height index at birth. In this paper, we attempt to assess the averaged teeth eruption terms in children born with macrocomia, taking into account weight, length and weight-height index of a newborn child.

The purpose of this research is to study the effect of body overweight at birth (macrosomia) on the processes of teeth eruption and of teeth growth during the first year of life, taking into account different values of the weight-height index at birth.

The research aims to perform the following tasks:

1. Based on extensive factual material, to confirm the correlation between the states (macrosomia/normosomia) of a child at birth and the terms (delayed/timely/premature eruption) of deciduous teeth eruption expressed in teeth quantity at the age of one year.
2. Depending on the value of the harmonious (well-balanced) development coefficient at birth, to detect the features of teeth eruption in children born with macosomia: for children with harmonious intrauterine development; with intrauterine accelerated growth and relatively low body weight; with intrauterine obesity on the background of large body length; and for children with intrauterine obesity on the background of the average body length.

MATERIAL AND METHODS

We carried out a retrospective analysis of 9,177 medical records of patients born between 1977 and 2013 and then treated in the First Department of the Municipal Children's Clinic number 23 in Kharkiv (Ukraine).

The Ethical and bioethical committee of the Kharkiv National Medical University (minutes No. 5 of 10 May 2016) confirms that the techniques used in this study have been applied with the respect to human rights in accordance with the current legislation in Ukraine, meet international ethical requirements and do not violate ethical norms in science and standards for conducting biomedical research.

All the patients have been divided into two groups in accordance with their weight-height indexes at birth. The Main Group included 748 children with fetal macrosomia (8.2% of the total number of studied medical records). There are 485 boys and 263 girls among them born within the normal term range of 37–42 weeks' gestation age. The Comparison Group involved 706 children (413 boys and 293 girls) born within the normal term range of 37 to 42 weeks' gestational age with height and weight corresponding to the gestational terms (fetal normosomia). The body weight at birth in this group is from 2,800 g to 3,799 g. The distribution of the number of medical records analyzed within the years, remained steady and comparable for both macrosomic and normosomic children of both sexes.

To determine possible features in the process of teeth eruption and teeth growth, all children of the Main Group have been divided into four subgroups in accordance with weight-height parameters at birth using the harmonious coefficient by V. I. Hryschenko et al. (15). These subgroups are presented in Figure 1.

Subgroup I consisted of medical records of the 247 macrosomic newborns (160 boys and 87 girls) with harmonious intrauterine development.

Subgroup II includs medical records of 96 macrosomic children (66 boys and 30 girls) who were born with long body height and relatively decreased intrauterine body weight.

Subgroup III is made up of medical records of 145 macrosomic children (104 boys and 41 girls) born with long body height and being overweight, which is classified by V. I. Hryschenko as the intrauterine acceleration in the background of obesity.

Subgroup IV is comprised of the medical records of 260 macrosomic children (154 boys and 106 girls) who were born with average weight parameters in combination with intrauterine obesity.

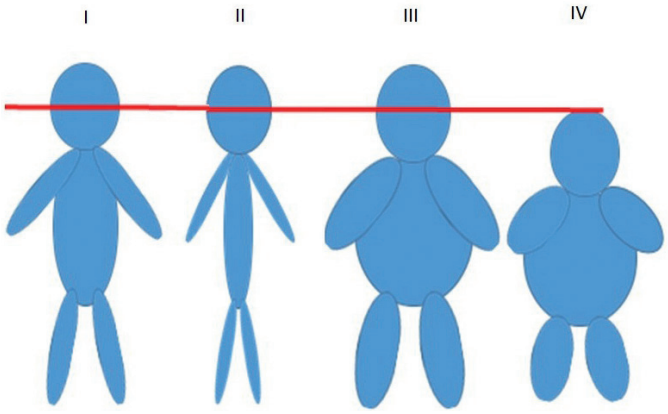

Fig 1 Schematic depicting of macrosomic newborns in subgroups (15), where *Subgroup I* children are long, harmoniously developed newborns; *Subgroup II* children are newborns with increased body length and relatively low body weight; *Subgroup III* children are newborns with intrauterine acceleration in combination with intrauterine obesity; *Subgroup IV* chidren are newborns with average body length and severe obesity.

Table 1 shows the average weight-height parameters of all the participants under study based on their body weight-height index at birth. The differences in the weight-height parameters between the groups and subgroups proved to be for the significance level, p, of less than 0.05.

Taking into account the scientific findings that breastfeeding has a significant impact on the craniofacial complex development; we have analyzed the medical records of the patients under study and found that 67% macrosomic and 64% normosomic children have been breastfed by the age of 6 months.

The degree of the maxillofacial area development is evaluated using the chronological norms of deciduous tooth eruption, i.e., using the number of teeth erupted before the age of one year (6). We calculated the percentage of the delayed or premature teeth eruption in all groups and subgroups with the respective confidence intervals and the significance level $p < 0.05$ for the binomial distribution law of the random value (16).

To determine the average term of first tooth eruption, as well as the deciduous teeth growth rate for each of the groups under the study, we have used the hypothesis about a linear dependence between the number of erupted teeth and the age of the child. Testing this hypothesis and defining the coefficient of the multiple linear regression have been performed with the STATISTICA 6.0 software package (Multiple Regression module). The coefficient of determination, B, (at a level of 0.6) is estimated from a regression fit, and the Pearson's chi-squared test is applied to evaluate the degree to which the distribution of residuals is consistent with the normal distribution (for the significance level, p, of less than 0.05). Student's t-test is used for assessing the statistic significance of the difference between the regression coefficients for different groups and subgroups for the significance level, p, of less than 0.05 (17).

RESULTS OF THE STUDY

We have analyzed the data from children medical records as to the number of teeth, which they had between the ages of 4 and 12 months. The data on girls and boys are calculated separately. Table 2 shows the amount of statistics for children with both fetal macrosomia and normosomia.

The records of baby age, measured in months, are almost uniformly distributed, and the distributions for macrosomic – normosmic child pairs for girls and boys are comparable. The difference in the number of records by a factor of 3 is less for all age groups.

The available data have been used for calculating the regression lines. The data obtained prove that the relationship between the dependent variable (number of teeth) and the predictor (age) is adequately represented by a linear regression. The determination coefficient is

Tab. 1 Average participant weight, height, head and chest circumference at birth with both fetal macrosomia and normosomia.

Groups and Subgroups	Body weight (kg)	Height (cm)	Head circumference (cm)	Chest circumference (cm)	Weight-height index (kg/m^3)
Normosomia (N = 706)	3.31 ± 0.02	51.79 ± 0.14	35.13 ± 0.10	34.32 ± 2.58	23.94 ± 0.21
Macrosomia (N = 748)	4.18 ± 0.01*	54.57 ± 0.16*	35.96 ± 0.22*	36.71 ± 2.75	26.20 ± 0.10*
Subgroup *I* (N = 247)	4.16 ± 0.02*	55.60 ± 0.16*	36.72 ± 0.65*	36.21 ± 4.83	24.19 ± 0.12
Subgroup *II* (N = 96)	4.16 ± 0.04*	58.34 ± 0.30*	36.65 ± 0.27*	36.19 ± 0.27	20.99 ± 0.24*
Subgroup *III* (N = 145)	4.35 ± 0.04*	54.38 ± 0.12*	36.99 ± 0.20*	36.54 ± 6.58	27.05 ± 0.17*
Subgroup *IV* (N = 260)	4.12 ± 0.02*	52.30 ± 0.11*	36.55 ± 0.18*	35.87 ± 0.35	28.88 ± 0.25*

* The difference between the macrosomic and normosomic children of the same gender is significant (within the 0.95 confidence interval).

Tab. 2 Sample sizes and parameters from linear regression analysis for the children with both fetal macrosomia and normosomia at birth.

Groups	Macrosomia		Normosomia	
Participants	**Boys**	**Girls**	**Boys**	**Girls**
Total number of medical records	483	265	413	293
Number of data in medical records for 4–12-month-old children	1,947	1,040	1,773	1,187
Average age the child has no teeth, month	5.18 ± 0.22	5.22 ± 0.35	5.07 ± 0.20	5.10 ± 0.27
Teeth growth rate, teeth per month	0.933 ± 0.016*†	0.829 ± 0.022*†	0.963 ± 0.014†	0.911 ± 0.018†
Average age the child has 1 tooth, month	6.25 ± 0.24	6.42 ± 0.38	6.11 ± 0.22	6.20 ± 0.29
Average number of teeth for 12-month-old children	6.37 ± 0.32	5.63 ± 0.42	6.67 ± 0.29	6.29 ± 0.37

* The difference between the macrosomic and normosomic children of the same gender is significant (within the 0.95 confidence interval).
† The difference between children of opposite sex in the same group is significant (within the 0.95 confidence interval).

significantly higher and varies in the 0.61–0.69 range for different subgroups.

The generalized results of calculations using the regression relations obtained and the corresponding confidence intervals for the significance level, *p*, of less than 0.05 are also presented in Table 2. The fifth row in Table 2 shows the average age until the child has no teeth.

The results obtained showed that eruption began during the first or second week of the sixth month from the birthday, i. e., until this age, teeth are absent on average. In boys, teeth began to erupt slightly earlier than in girls, but this difference is within the confidence interval. These results agree with the results of other researchers (18).

The differences in the teeth growth rate in girls and boys with both fetal macrosomia and normosomia at birth are under consideration now. The sixth row in Table 2 shows that the average teeth growth rate in the macrosomic children is less than in the normosomic ones with an error probability that does not exceed 0.05. This is true for the children of both sexes, and the teeth growth rate in both macrosomic and normosomic girls, in turn, is significantly lower than in boys.

The last two rows in Table 2 give reference information about the average age when a child has one tooth, as well as the average number of teeth at the age of one year for the children of each group. These facts occur with a delay both in boys and girls of the macrosomic group, as compared to the normosomic. Unfortunately, it is impossible to confirm the validity of these differences.

The regression analysis suggests a normal distribution of the residuals. We have constructed and analyzed the histograms showing the distribution of the residuals. The Pearson's chi-squared test confirmed that the distribution of residuals is consistent with the normal distribution for the significance level, *p*, of less than 0.05. Thus, the validity of linear regression analysis applicability to our research is additionally confirmed.

The next task is to consider the differences in terms of teeth eruption and deciduous tooth growth rate in Main Group (macrosomic children) taking into account weight-height parameters at birth. This has been achieved by calculating the regression lines for every subgroup and gender. Table 3 shows the total amount of records containing the number of erupted teeth in children of different sexes born with macrosomia and normosomia. The data in Table 3 colomns are presented in accordance with their body length and weight-height index at birth and gender.

Given in Table 3 are summarized calculations for these regression models. On average, there is a tendency for a later teeth eruption in macrosomic children in all subgroups as compared with normosomic ones of the same sex, which agrees with the results obtained by Khurasseva (13), as can be seen in the fifth row in Table 3. In macrosomic boys teeth began to erupt on average of 0.1–0.2 months earlier than in girls. This is true for all subgroups, except for *Subgroup I*. But this difference is unreliable and is within the confidence interval. Teeth eruption occurs in boys in *Subgroup IV* before it occurrs in all other macrosomic children, almost in the same terms as in normosomic children.

The most interesting differences in the teeth growth rate are found between macrocomic and normosomic subgroups. Table 3 (sixth row) shows that the teeth growth rate in all macrosomic children is slower than in normosomic, except for girls in *Subgroup III*. The teeth growth rate in boys with macrosomia is slower than that in normosomic boys, and the difference for different subgroups is 0.02–0.14 tooth per month. In *Subgroups II* and *III* this difference is reliable within the 95% confidence interval.

The teeth growth rate in girls with macrosomia is also slower than that in girls with normosomia, except for girls from *Subgroup III*. The difference for variuos subgroups is 0.72–1.17 tooth per month. It is reliable within the 95% confidence interval.

It is also important to pay attention to the fact that within the subgroups the teeth growth rate in boys is faster than in girls, except for *Subgroup III*. For children in *Subgroups I* and *IV* this difference is significant (for the significance level, *p*, of less than 0.05).

The seventh row in Table 3 proves that the average age of the first tooth eruption in a macrosomic child falls within the 6.15–6.65-month interval, and it falls within the 6.11–6.20-month interval in a normosomic child. In other words, there is a tendency for a later beginning of teeth eruption in all subgroups of macrosomic children, although the 0.95 confidence intervals overlap. Moreover, the average age of the first tooth eruption is slower in boys than in girls.

The last row in Table 3 shows that the mean number of teeth in one-year-old boys at the significance level of

Tab. 3 Sample sizes and multiple linear regression analysis for the children from different ranks.

Groups and subgroups	Subgroup I		Subgroup II		Subgroup III		Subgroup IV		Normosomia	
Participants	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls
	160	86	65	31	104	42	156	104	413	293
Number of samples in medical records for 4–12 month-old children	729	374	231	123	427	140	681	512	1,773	1,187
Average age the child has no teeth, month	5.22 ± 0.38	5.14 ± 0.57	5.16 ± 0.71	5.38 ± 0.98	5.16 ± 0.48	5.12 ± 1.04	5.10 ± 0.34	5.30 ± 0.50	5.07 ± 0.20	5.10 ± 0.27
Teeth growth rate, teeth per month	0.959 ± 0.028 †	0.839 ± 0.037*†	0.822 ± 0.044*	0.796 ± 0.059*	0.917 ± 0.032*	0.992 ± 0.077	0.960 ± 0.025†	0.793 ± 0.030*†	0.963 ± 0.014†	0.911 ± 0.018†
Average age the child has 1 tooth, month	6.26 ± 0.41	6.34 ± 0.62	6.38 ± 0.78	6.65 ± 1.08	6.26 ± 0.52	6.13 ± 1.11	6.15 ± 0.37	6.56 ± 0.54	6.11 ± 0.22	6.20 ± 0.29
Average number of teeth at the age of one year	6.52 ± 0.56	5.78 ± 0.73	5.66 ± 0.89	5.33 ± 1.17	6.29 ± 0.67	6.91 ± 1.56	6.63 ± 0.50†	5.33 ± 0.59*†	6.67 ± 0.29	6.29 ± 0.37

* –The difference between the macrosomic and normosomic children of the same gender is significant (within the 0.95 confidence interval).
† –The difference between children of opposite sex in the same Subgroup is significant (within the 0.95 confidence interval).

$p < 0.05$ is greater than that for girls for all macrosmic and normosomic subgroups, excluding *Subgroup III*. The macrosomic children have more teeth than the normosomic children of the same sex. The girls exhibit this difference reliably in *Subgroups I* and *IV*, while the boys show it in *Subgroup II*. The macrosomic girls in *Subgroup III* are the exception: they have more teeth than the normosomic girls, which is in agreement with the results obtained by Suri L. and co-authors (1).

The above-mentioned results reflect the statistically average differences in teeth eruption terms up to 1 year on the basis of the data of the number of teeth in the medical records. However, there is another approach to assessing the teeth eruption terms based on comparison with the regional chronological norm of eruption. The chronologic delay of deciduous teeth eruption is considered to be an eruption that occurs later than 2 standard deviations from the mean of the regional norm for eruption time in the population (6). Conversely, a chronologic premature eruption is considered to be an eruption, which occurs earlier than 2 standard deviations from the mean of the regional norm for eruption time in the population. In our study, if the first tooth eruption occurred at the age of 4 months or earlier, it is recorded as a premature teeth eruption. If the first tooth eruption occurred in 11 months old child, or later, it is recorded as a delayed eruption.

In addition, using 2 standard deviations from the median number of teeth in one-year-old children in the Kharkiv population, we have calculated the number of teeth that a child had at one-year-old age. If a child, after reaching this age, has 2 or less teeth, a slow teeth growth rate is recorded. If a child had 11 or more teeth, the teeth growth rate is accelerated. Table 4 provides information on the number of cases of delayed eruption, premature eruption, cases of slow and accelerated teeth growth rate, separately for girls and boys in different groups and subgroups, using regional chronologic norms. Table 4 also presents the corresponding occurrence rates calculated for the binomial distribution law of the random variable and their confidence intervals for the significance level, p, of less than 0.05.

Table 4 shows that in the macrosomic children, the percentage of detected cases of delayed teeth eruption is greater than in the normosomic group by a factor of almost 4. Subcategorisation shows significant differences for girls in *Subgroup IV*, as well as for boys in *Subgroup I* and *II*. The percentage of cases of premature teeth eruption in macrosomic children is also greater than that in normosomic ones by a factor of approximately 2. Nonetheless, the confidence intervals for the given significance level of $p < 0.05$ overlap. A true increase is found only for girls in *Subgroup III*.

Such significant deviations from regional norms for the number of delays and premature teeth eruption in macrosomic children can be attributed to various causes that led to the macrosomia formation and to extremely different weight-height parametres at birth.

As shown above, the children in *Subgroup I* confirm their name "harmoniously developed". The age when teeth begin to erupt, the age when the child has 1 tooth, and the average number of teeth in these children at the age of 1 year, practically do not differ from indices in normosomic children. In addition, we do not observe extreme values of any indicators listed in Table 4 in children in this subgroup. In other authors' studies (19), this group is conventionally termed "true accelerates".

The children in *Subgroup II* have the slowest tooth growth rate and the least number of teeth at the age of 1 year from all participants in the study (Table 3). In comparison with others, in this subgroup also are the highest percentage of boys with delayed teeth eruption and the highest percentage of children of both sexes who had 2 or less teeth at the age of 1 year. In our opinion, the relatively insufficient body weight, which these children have during intrauterine period, the same period when the anlage and formation of deciduous teeth and partially permanent

Tab. 4 Numerical data (numbers, percentage, confidence interval (CI)) on tooth eruption terms and the number of teeth in one-year-old children.

Groups and subgroups	Delayed teeth eruption		Premature teeth eruption		Two or less teeth at the age of 1 year		11 or more teeth at the age of 1 year	
Participants	Girls (number; %, CI)	Boys (number; %, CI)	Girls (number; %, CI)	Boys (number; %, CI)	Girls (number; %, CI)	Boys (number; %, CI)	Girls (number; %, CI)	Boys (number; %, CI)
Normosomia (413 boys, 293 girls)	7; 2.4%; 1.2% – 4.4%	6; 1.5%; 0.7% – 2.8%	5; 1.7% 0.8% – 3.5%	7; 1.7% 0.8% – 3.1%	16; 5.5% 3.4% – 8.3%	14; 3.4% 2.0% – 5.3%	8; 2.7% 1.4% – 4.9%	6; 1.5% 0.7% – 2.8%
Macrosomia (485 boys, 263 girls)	24; 9.1% 6.2% – 12.8%*	29; 6.0% 4.2% – 8.2%*	9; 3.4% 1.8% – 5.9%	16; 3.3% 2.1% – 5.0%	13; 4.9% 2.9% – 7.8%	17; 3.5% 2.2% – 5.3%	7; 2.7% 1.3% – 4.9%	10; 2.1% 1.1% – 3.5%
Subgroup I (160 boys, 86 girls)	6; 7.0% 3.3% – 13.0%	12; 7.5% 4.4% – 12.0%*	2; 2.3% 0.7% – 6.3%	4; 2.5% 1.0% – 5.4%	3; 3.5% 1.3% – 8.1%	7; 4.4% 2.2% – 8.0%	2; 2.3% 0.7% – 6.3%	3; 1.9% 0.7% – 4.4%
Subgroup II (65 boys, 31 girls)	3; 9.7% 3.6% – 21.4%	5; 7.7% 3.5% – 15.0%*	1; 3.2% 0.8% – 11.2%	2; 3.1% 1.0% – 8.3%	3; 9.7% 3.6% – 21.4%	4; 6.2% 2.5% – 12.9%	0; 0% 0% –11.2%	1; 1.5% 0.4% – 5.5%
Subgroup III (104 boys, 42 girls)	3; 7.1% 2.7% – 16.2%	5; 4.8% 2.1% – 9.6%	4; 9.5% 4.0% – 19.5%*	3; 2.9% 1.1% – 6.8%	2; 4.8% 1.5% – 12.6%	4; 3.8% 1.6% – 8.2%	1; 2.4% 0.6% – 8.4%	4; 3.8% 1.6% – 8.2%
Subgroup IV (156 boys, 104 girls)	12; 11.5% 6.8% – 18.1%*	7; 4.5% 2.2% – 8.2%	3; 2.9% 1.1% – 6.8%	9; 5.8% 3.1% – 9.9%*	5; 4.8% 2.1% – 9.6%	2; 1.3% 0.4% – 3.5%	4; 3.8% 1.6% – 8.2%	3; 1.9% 0.7% – 4.6%

* The difference between the macrosomic and normosomic children of the same gender is significant (within the 0.95 confidence interval

teeth occur, could contribute to the above violation. The results obtained to some extent coincide with the results published by Sajjadian N. and co-authors (3), which indicate that the birth weight and the age of first tooth eruption are directly proportional. The research conducted also suggests that the low weight-height index at birth in children of this subgroup correlates with delayed eruption.

The children from *Subgroup III* show the most deviant results. Despite the fact that boys of this subgroup have a significantly lowered teeth growh rate (Table 3), they also have the highest percentage of having 11 or more teeth at the age of 1 year among all the children. The girls of this subgroup exhibit the highest teeth growth rate among all participants in the study. Moreover, their teeth growth rate is significantly higher than that of normosomic children, with the highest percentage of preterm teeth eruption among all subgroups.

Subgroup IV is comprised of children with intrauterine obesity. Despite the averaged metrics for children in *Subgroup IV* and in the group of normosomic boys are comparable, as can be seen in Table 4, the macrosomic boys have a significantly higher percentage of premature teeth eruption among all participants in the study, as can be seen in Table 5. The girls in this subgroup have the slowest teeth growth rate, as compared to others, the smallest number of teeth at the age of 1 year (Table 3) and the highest percentage of delayed teeth eruption. We can assume that the intrauterine obesity in combination with the average or large weight-height indexes has a different effect on the teeth formation in children of different sexes.

DISCUSSION

The reasons for the differences in the tooth growth process in first-year macrosomic children remain studied incompletely. However, the hormonal system dominance in this prosses is obvious. Macrosomic children with different somatotypes have some hormonal system features that were previously studied by the pathologists at Kharkiv National Medical University (15, 19). We have repeatedly mentioned in this paper the difference in terms of teeth eruption and the deciduous tooth growth rate in macrosomic children of different sexes, which can also be ascribed to sex hormones providing better developed muscle system in boys than in girls. This aspect requires further research.

The studies (20, 21) we have conducted earlier have revealed hypoplastic processes in the minor and parotid salivary glands in macrosomic at birth experimental animals, and the delayed tooth eruption revealed in this study in macrosomic at birth children suggests that the hypoplastic process is a generalized process, and a significant cell division inhibition during intrauterine period in case of fetal macrosomia occur. The cases of premature tooth eruption can be explained by axceleration processes.

Data about the deviation from the generally accepted terms of teeth eruption in children born with macrosomia, taking into account different weight-height rates at birth, can explain differences in existing publications.

When analyzing the health state of the children in the first year of life, non-invasive diagnosis is used. Among the commonly accepted developmental criteria (body weight, body length, head circumference, chest circumference), the criteria are used that indicate the parity, sequence and symmetry of deciduous teeth eruption, as well as the averaged regional terms of their eruption. In this way, the data we obtain may be of interest to pediatricians and pediatric dentistry.

All dental preventive procedures and treatments are based on the knowledge of the exact timing of eruption, formation and resorption (in the case of deciduous teeth) of the root system of the teeth. Our observations and observations made by other authors indicate that children born with macrosomia have high caries intensity of deciduous teeth (4, 22, 23). Taking into account the delayed or premature eruption recorded in our study and the

slowered growth rates of deciduous teeth in children, macrosomic at birth, we can assume a low mineralization of hard tooth tissue in this sample of children. Consequently, the prevention of caries in them should begin earlier than usual, namely, from the moment of the first tooth eruption onward. That multiplicity of examinations by children's dentist should be increased. Carious lesions, including the caries of the approximal surfaces of the teeth, in turn, lead to a shortening of the dentition (23), and as a consequence, the progenia or prognatism formation. That is, the average terms of initiation of orthodontic prophylactic procedures, which are usually carried out in a child at the age of 3 to 4 years, should begin earlier in these children.

When the parents of a child, whose parameters at birth were higher than the norm, consult a doctor, the doctor should propose a certain algorithm for taking preventive care or providing treatment. Information about the somatometric indices of the macrosomic child at the time of birth, namely, the weight-height index and the body length, make it possible to predict the averaged terms of deciduous teeth eruption and can significantly simplify the diagnostic process, make it useful when diagnosing and timely (which is very important) prescribing treatment and preventive care individualized for each specific child.

CONCLUSION

1. The retrospective statistical study of data accumulated over a 30-year period have confirmed that there are differences in the process of odontogenesis in both girls and boys born macrosomic in comparison with children whose parameters correspond to the regional norms. The features considered include a slow deciduous teeth growth rate in children born with macrosomia and an increased frequency (by a factor of 2 to 4 times) of deviations in the timing of teeth eruption compared to regional norms.
2. In macrosomic boys with harmonious intrauterine weight and height parameters, the desiduous teeth growth rates are close to the corresponding index in the *Comparison group*. In girls in this group, the teeth growth rate is significantly slower.
3. In macrosomic children born with a long body and with relatively decreased intrauterine body weight, tooth growth rate is significantly slower as compared to normosomic children. In addition, we have singled out a significantly higher percentage of delayed teeth eruption in the boys of this subgroup.
4. The teeth growth rate in macrosomic boys born with long body in combination with intrauterine obesity, is significantly slower than that in the *Comparison group*. For girls, the result turned out to be the opposite.
5. Macrosomic boys with intrauterine obesity and average body weight at birth have a significantly higher percentage of premature teeth eruption. Instead, macrosomic girls show a significantly slower tooth growth rate and a higher percentage of delayed teeth eruption.
6. The exact timing of eruption, formation and resorption of deciduous teeth in macrosomic at birth children, are criteria for general and dental health. These data can significantly simplify the diagnostic process, they are simple, cheap, and non-invasively obtained (in contrast to X-ray examination and general blood count), which, in case of children, is extremely important.

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Non-Recurrent Right Laryngeal Nerve: a Rare Anatomic Variation Encountered During a Total Thyroidectomy

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ABSTRACT

The non-recurrent laryngeal nerve (nRLN) is a rare anatomic variation that every head and neck surgeon must be aware of, in order to avoid intraoperative injury which leads to postoperative morbidity.

We are reporting a case of a nRLN in a 47 year old female patient with medullary thyroid carcinoma who was surgically treated with total thyroidectomy and lymph node dissection. Both two inferior laryngeal nerves were identified, fully exposed and preserved along their cervical courses. However, we found that the right inferior laryngeal nerve was non-recurrent and directly arised from the cervical vagal trunk, entered the larynx after a short transverse course and parallel to the inferior thyroid artery.

The safety of thyroid operations is dependent on high index of suspicion, meticulous identification and dissection of laryngeal nerves either recurrent or non-recurrent. This leads to minimum risk of iatrogenic damage of the nerves.

Complete knowledge of the anatomy of these neural structures, including all their anatomic variations is of paramount importance.

KEYWORDS

non-recurrent laryngeal nerve; thyroidectomy; vagus nerve

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INTRODUCTION

The recurrent laryngeal nerve (RLN) innervates the intrinsic muscles of the larynx except the cricothyroid. The typical course of RLN is to ascend on either side of the trachea and enter the larynx just lateral to the ligament of Berry. On the right side, the recurrent laryngeal nerve separates from the vagus as it crosses the subclavian artery, passing posteriorly and ascending in a lateral position to the trachea along the tracheoesophageal groove. While on the left side, the recurrent laryngeal nerve separates from the vagus as it traverses over the arch of the aorta.

The nonrecurrent laryngeal nerve (nRLN) is a rare anatomical variation, of the recurrent laryngeal nerve (RLN) that takes an aberrant course and not descending into the thorax (1). The incidence of nRLN in thyroid surgery has been reported from 0.3 to 1% on the right side, while it is extremely rare on the left side (0.004%) (2).

The nRLN is consistently related to the absence of brachiocephalic trunk and the presence of the so-called arteria lusoria resulting in an aberrant subclavian artery that runs behind the esophagus on the right side. It only appears on the left side if associated with situs inversus (3). The existence of a nRLN without the associated vascular anomalies has no clear embryological explanation (1).

CASE REPORT

A 47-year old woman with no known medical history or chronic illnesses presented to our Department with a right-sided thyroid nodule for one year. She had no complaints of hoarseness or compressive symptoms. On examination, the right lobe of the thyroid was found to be enlarged. An indirect laryngoscopic examination showed normal vocal cord function. Ultrasound revealed a solitary, solid 0.82 × 0.71 cm nodule in the right lobe. There were no cervical nodes seen on ultrasound. However Calcitonin levels were remarkably high (22.7 pg/ml). She was confirmed to be euthyroid (TSH 3.2 mU/l) and (FT4 12.0 pg/ml). The patient underwent fine needle aspiration and opted for a total thyroidectomy and lymph node dissection ipsilateral and contralateral in central compartment VI. The nerve on the left side was found in the left tracheoesophageal groove in a recurrent fashion, where as in the right side the thyroid lobe was rotated medially and the right laryngeal nerve was not recurrent as it was not found as expected in or near the tracheoesophageal groove. However, careful exploration revealed a transverse nerve running medially to the cricothyroid joint parallel and superficial to the trunk of the inferior thyroid artery (Fig. 1, 2) The nerve was preserved without damage. Histopathological evaluation revealed medullary carcinoma. The postoperative period was uneventful and the patient had no change in her voice. Histopathology revealed two foci of papillary carcinoma 0.3 cm and 0.1 cm in the lower pole of the right lobe. Hashimoto thyroiditis was also remarkable. Neoplasia of the parafollicular cells C, with positive Calcitonin antibodies was also revealed. Lymph nodes were infiltrated from papillary carcinoma with immunohistochemistry positive for TTF-1. No infiltration in twelve lymph nodes of the right central compartment and no infiltration in eight yielded lymph nodes of the left central compartment, was found. Follow-up with CT of the chest, MRI of the liver, bone scintigraphy and Calcitonin, CEA levels were within normal range.

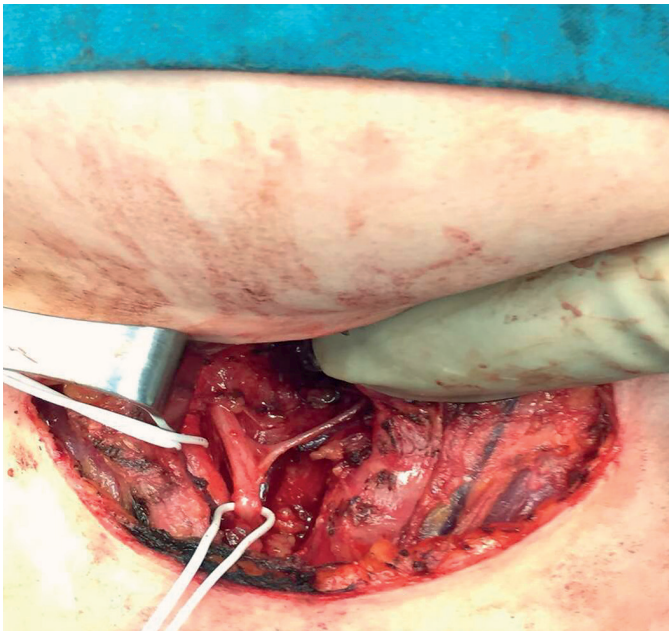

Fig. 1 Right side view of a patient with nRLN during total thyroidectomy. The vagus trunk is medially and superficially located to the common carotid artery.
(CCA: Common Carotid Artery, VN: Vagus Nerve, nRLN: non-Recurrent Laryngeal Nerve, ESO: Esophagus, TR: Trachea)

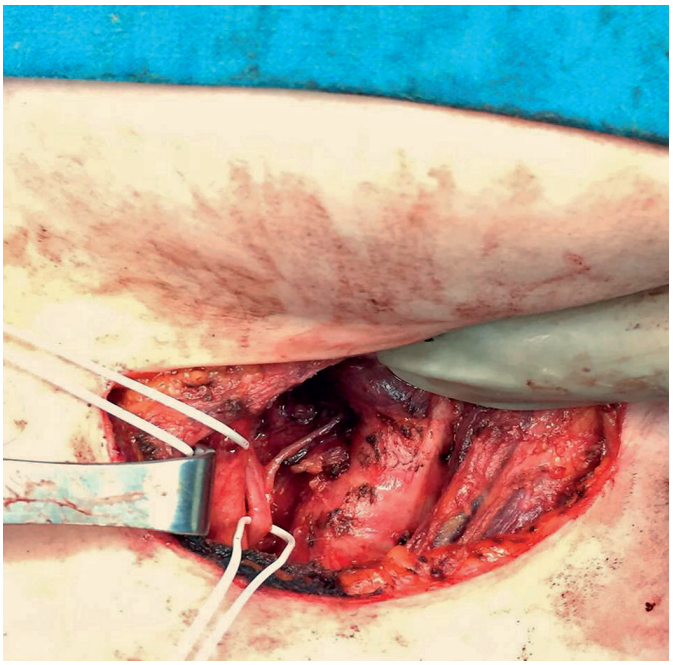

Fig. 2 Right lateral view of a patient undergoing total thyroidectomy. The right non-recurrent laryngeal nerve arises directly from cervical vagus trunk and enters the larynx just parallel to the inferior thyroid artery (Type 2A). The inferior thyroid artery is ligated.
(CCA: Common Carotid Artery, VN: Vagus Nerve, nRLN: non-Recurrent Laryngeal Nerve, CM: Cricopharyngeal Muscle, TR: Trachea)

DISCUSSION

The nRLN anatomic variation was first reported by Steadman in 1823, in a cadaver, along with an anomaly of the origin and course of the right subclavian artery (4).

The origin of the nRLN is cervical and there are three types reported (4).

Type 1 occurs when the nRLN arises directly from the vagus and travels with the superior thyroid pedicle vessels. Type 2 is further divided into subtypes A and B.

In Type 2A, the nRLN travels transversely, parallel and superficial to the trunk of the inferior thyroid artery and Type 2B occurs when the nerve travels in a transverse path parallel, but deep to or between the branches of the inferior thyroid artery. Our case can be described as a Type 2A nRLN.

A nRLN can be injured intraoperatively and this may lead to long-term postoperative complications such as vocal cord paralysis. Adequate identification dissection and isolation is very important for preventing damage (1).

In a systematic review by Henry B et al, an overall pooled prevalence of right nRLN of 0.7% was reported in the general population.

The embryological pathogenesis of an nRLN with an aberrant subclavian artery is clear and understood, but the presence of the variant nerve without the accompanying vascular anomaly, like in our case, remains to be elucidated.

In the literature, Li X et al have dissected 821 recurrent laryngeal nerves, during 2496 thyroid operations, from which 5 were confirmed to be nRLN (0.61%) (5).

Henry JF et al reported 33 cases of nRLN in 6307 cervicotomies for thyroid and parathyroid operations (0.52%). The anomaly was observed in 31 cases from 4921 dissections on the right side (0.63%) and in two cases from 4673 dissections on the left side (0.04%) (6).

The nRLN was encountered in a study only after performing 585 thyroid operations in three years with an overall incidence of 0.2% (7). Others have reported a small recurrent laryngeal nerve with a major non-recurrent trunk (7, 8).

CONCLUSIONS

Non-recurrent laryngeal nerve incidence is very rare. When encountered there is a high risk of iatrogenic injury during thyroidectomy or head and neck operations in general. Preoperative diagnosis can only be suspected when there is situs inversus or arteria lusoria. The present case, reports a patient without a vessel anomaly and nRLN was an incidental find during total thyroidectomy for medullary carcinoma.

We decided to present this case because it highlights this anatomical variant. Awareness of its existence and correct surgical technique can minimize the morbidity of iatrogenic damage of the inferior (recurrent or non-recurrent) laryngeal nerve.

CONSENT

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Abnormal Persistence of Embryonic Blood Supply of Liver: Anatomist's Delight, Surgeon's Nightmare

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ABSTRACT
The high incidence of hepato-biliary vascular anatomy variations necessitates its evaluation prior to performing liver transplantation, hepatobiliary, pancreatic, gastric and oesophageal surgeries. We report a unique case of persistence of embryonic arteries of the liver, wherein, the liver was supplied by five vessels. In addition to the usual right and left hepatic arteries from the hepatic artery proper, the liver received two accessory right hepatic arteries, one from the gastroduodenal artery, while another arising from superior mesenteric artery and an accessory left hepatic artery, from the left gastric artery. The origin of gastroduodenal artery was found to be unusually high and its abnormal anterior course over the common bile duct further added complexity to the hepatobiliary anatomy. The presence of these aberrant and accessory arteries predisposes to inadvertent injury leading to patient morbidity and sometimes mortality.

KEYWORDS
common hepatic artery; proper hepatic artery; accessory hepatic artery; gastroduodenal artery

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INTRODUCTION

The celiac trunk (CT) arises from abdominal aorta at the level of 12th thoracic vertebra, passes almost horizontally forwards for 1 to 3 cms. It trifurcates into left gastric artery (LGA), common hepatic artery (CHA) and splenic artery (SA) (1). While the LGA and SA run towards the left to supply the esophagus and spleen respectively, the CHA passes antero-laterally above the superior border of pancreas to the right as far as the first part of duodenum (1). After the origin of gastroduodenal artery (GDA), CHA continues as the hepatic artery proper (HAP). The HAP runs within the free margin of lesser omentum, where it lies anterior to portal vein (PV) and medial to common bile duct (CBD). It ends by dividing into right and left hepatic arteries at variable distance from the porta hepatis (1). Anatomical variations in the blood supply of liver and hepatic arteries are found in one third of the individuals (2, 3). The knowledge of variations in the origin of arteries supplying the liver is very important to perform surgeries like pancreaticoduodenectomy and liver transplant as well as during hepatic artery infusion chemotherapy (4). Due to occurrence of these variations it is imperative to map the individual specific arterial patterns by performing CT angiograms/ MR angiograms prior to undertaking major hepato-pancreatic-biliary surgical procedures (5). On table, during surgeries these variations increase the potential risk of complications like haemorrhage, liver necrosis, ischemia and are the foremost reasons for conversion of laparoscopic procedures to open surgery.

CASE REPORT

Routine abdominal dissection for undergraduate teaching in the Department of Anatomy at Maulana Azad Medical College, of 88 year old female with previous surgical history of right mastectomy only, revealed multiple variations in the branches of coeliac trunk and superior mesenteric artery. There were five hepatic arteries, each originating from a different source supplying the liver.

The CT had normal origin from the ventral aspect of abdominal aorta, at T12 vertebral level between aortic hiatus and the superior border of pancreas. Immediately after origin it gave rise to the right & left inferior phrenic arteries (IPA). The IPA had usual course and distribution thereafter. While the right IPA ran posterior to the inferior vena cava, the left IPA passed behind the esophagus, to supply the respective side of diaphragm & suprarenals. The left IPA also supplied the abdominal part of the esophagus (Fig. 1).

The CT branched in to usual three branches LGA, SA and CHA. CHA (length 4.5 cm) ran upwards over the first part of duodenum and gave rise to GDA and continued as HAP. The origin of GDA was unusually higher, approximately 4 cm from the pylorus. The GDA then turned sharply downwards from its origin and was present on the left side of CBD initially. Further distally, it took a C shaped curve anterior to the CBD, thereafter running posterior to the first part of duodenum where it divided into right gastroepiploic and anterior pancreatic duodenal artery. There was presence of pancreatic tissue between the GDA and

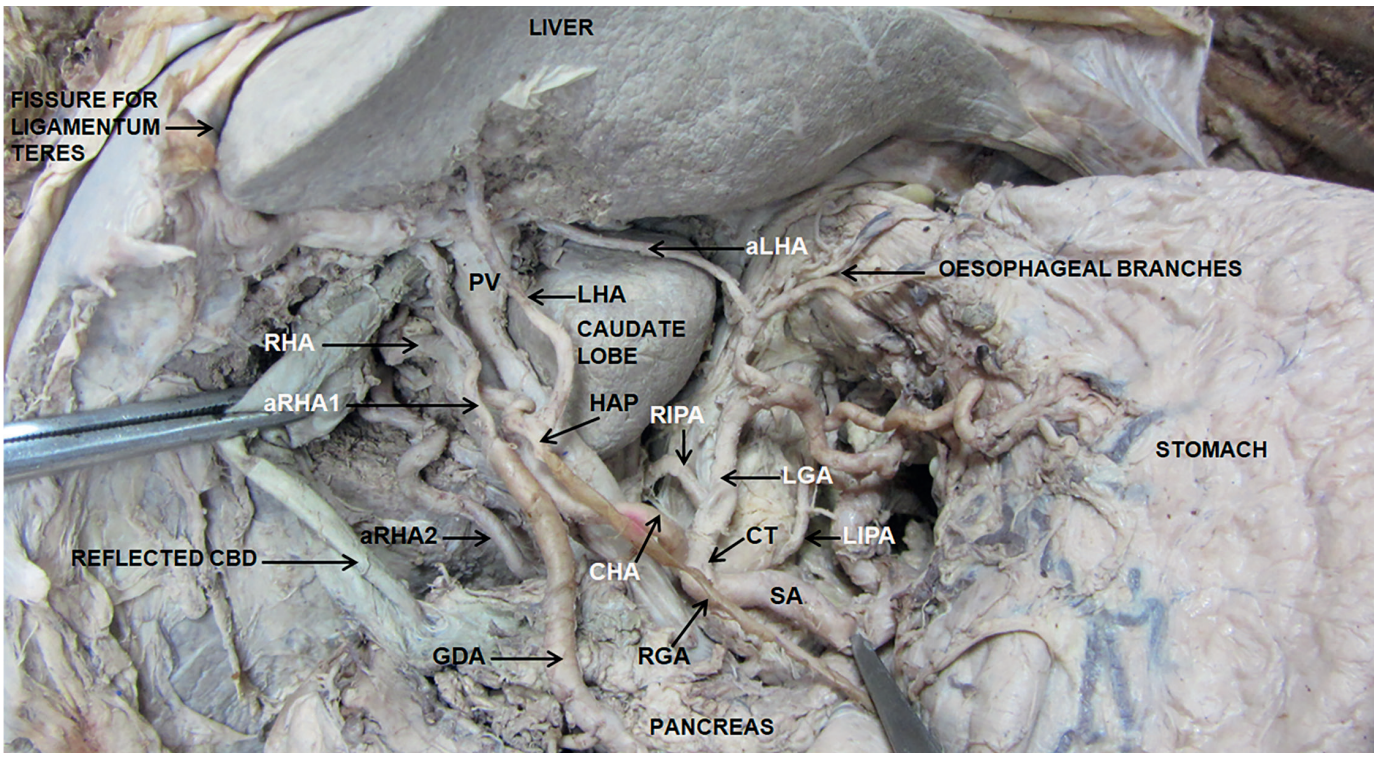

Fig. 1 A dissected specimen of abdomen: The celiac trunk (CT) dividing into three branches – Left gastric artery (LGA), Splenic artery (SA) and Common hepatic artery (CHA). Right inferior phrenic artery (RIPA) and Left inferior phrenic artery (LIPA) also originating from CT. CHA gives rise to high rising Gastroduodenal artery (GDA) and a small stump of Hepatic artery proper (HAP). HAP divides into Right hepatic artery (RHA) and Left hepatic artery (LHA). LGA gives rise to Accessory left hepatic artery (aLHA). The Common Bile Duct (CBD) has been retracted to clearly visualise One Accessory right hepatic artery (aRHA1) arising from GDA while another Accessory right hepatic artery (aRHA2) arising from superior mesenteric artery.

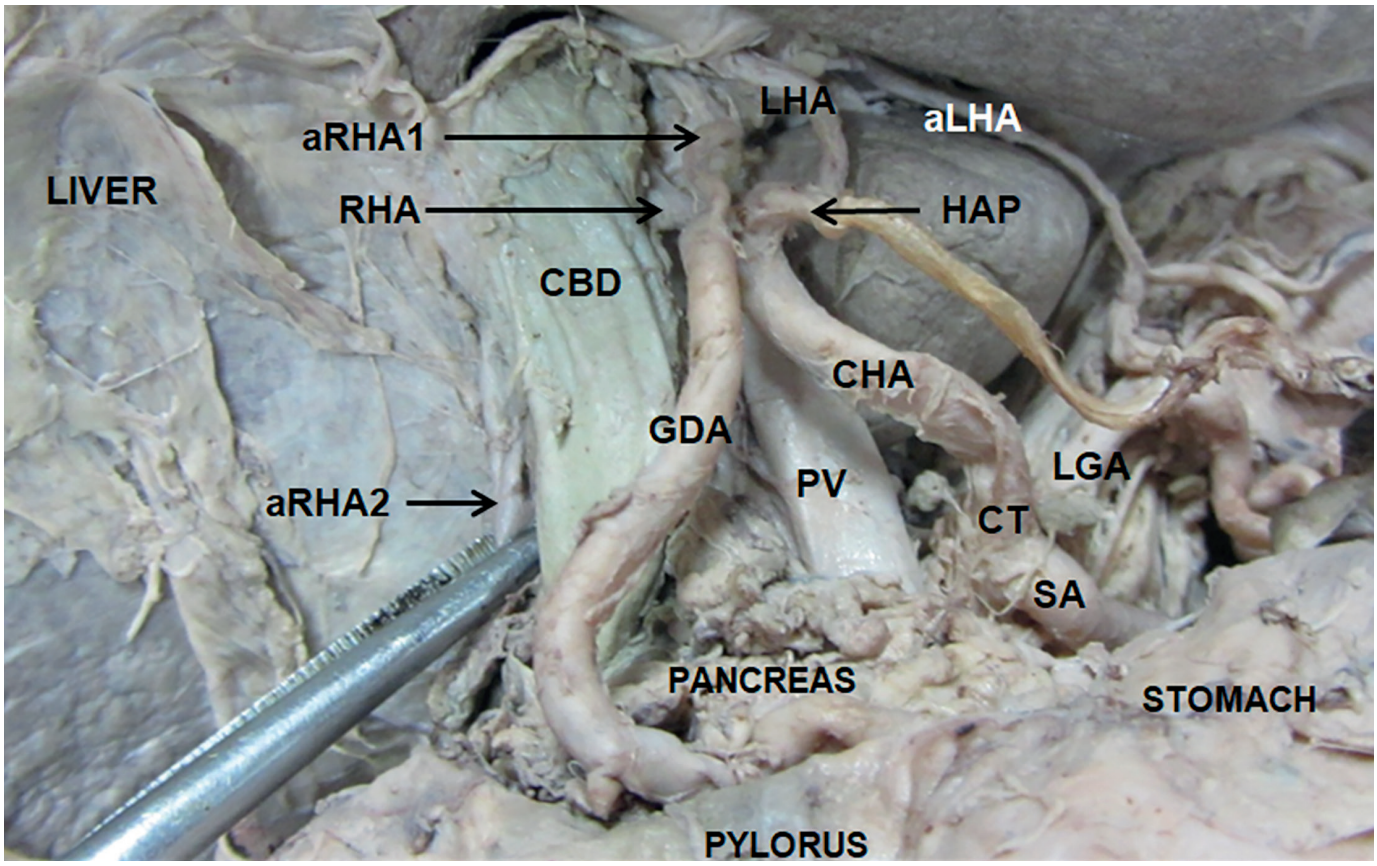

Fig. 2 Depicting High origin of gastroduodenal artery (GDA) and relation of GDA and accessory right hepatic artery (aRHA2) with common bile duct (CBD). Note the C shaped mid and distal portion of GDA present anterior to the CBD with a small portion of pancreas intervening in between.

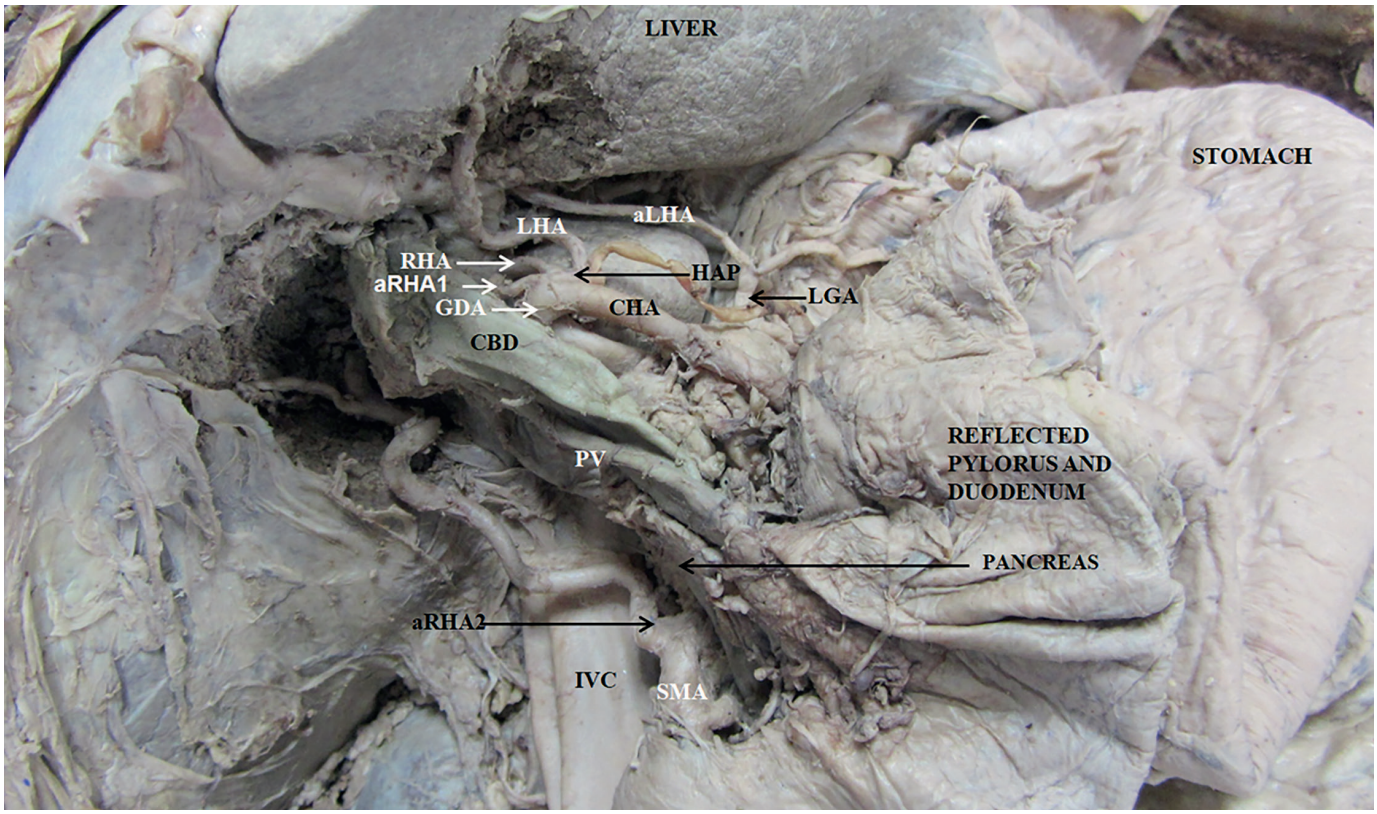

Fig. 3 Showing origin of accessory right hepatic artery (aRHA2) from superior mesenteric artery (SMA) behind the head of pancreas.

CBD only near the pylorus. The first accessory right hepatic artery (aRHA1) arose from the GDA where it turned sharply to descend to the left of CBD (Fig. 1, Fig. 2).

HAP was present as a small stump (0.4 cm). It gave rise to the right gastric artery (RGA) proximally and then bifurcated into the right hepatic artery (RHA) and left hepatic artery (LHA). The RHA passed obliquely upwards for 3 cm, anterior to the PV and posteriomedial to hepatic duct to enter into porta hepatis. It was crossed anteriorly by aRHA1 from right to left (Fig. 1, Fig. 2). Another accessory right hepatic artery (aRHA2) was seen arising from SMA posterior to the pancreas. It travelled posterior to the CBD and to the right of aRHA1 (Fig. 3). LHA ascended for about 2.4 cm to enter the porta hepatis, on the left side of fissure for ligamentum teres and supplied the left lobe of liver. There was an accessory left hepatic artery (aLHA), a branch of LGA, which entered the anatomical left lobe of the liver medial to the PV (Fig. 1, Fig. 2). Thus at the porta hepatis LHA and aRHA1 were to the left of the bile duct, while RHA and aRHA2 were posterior to it. Posterior most structure was the portal vein. RHA and aRHA2 were lateral to it and aLHA entered the liver medial to PV. Near the superior border of the pylorus and first part of duodenum, the CBD was sandwiched between GDA anteriorly and aRHA2 posteriorly (Fig. 2).

DISCUSSION

Embryologically there are three lobes during development of mammalian liver – right lateral, central and left lateral lobes. Each of these has its own embryonic arteries supplying it. The left hepatic artery arises from the LGA and supplies the developing left lateral part of the liver. The right lateral anlage is supplied by a branch arising from SMA and the central lobe by the proper hepatic artery, arising from the junction of CHA and GDA, branches of CT. These arteries anastomose in the developing liver to supply the viscera. During the early embryonic stages, the developing liver anlage is larger than the developing gut. Later on the size of the liver proportionately decreases while that of the gut increases. Also the enlarging stomach and the spleen further reduce the size of the left lobe. These rearrangements cause regression and shifting of these three embryonal arterial roots results in the final single hepatic artery becoming the predominant artery supplying the liver. However variable persistence/absorption of the vessels result in anomalous vasculature (6). In the present case liver was supplied by five branches – the usual, RHA and LHA branches of a small stump PHA and additional aRHA1, branch of GDA, aRHA2 arising from SMA and aLHA, branch of LGA. Thus, all three embryonal arterial roots persisted as aRHA2, aLHA and middle vessel as PHA (although a short one) and supplied the liver (6) (Fig. 4). However this fails to explain the presence of an aRHA1 from GDA and the IPAs arising from the CT. These could be the remnant one of the branches of Tandlers longitudinal anastomosis which develops between the ventral abdominal aortic branches supplying the gut (7) (Fig. 4). Not only were accessory and aberrant branches present, the course of these vessels was also variable. The GDA branched out from the CHA higher than usual – 4 cm above the pylorus. At the porta hepatis LHA and aRHA1 were to the left of the bile duct, while RHA and aRHA2 were posterior to it. In its lower part the GDA took a C shaped curved bend over the CBD.

Michel's classification for hepatic artery describes a number of variants. However the present case does not fall under any of the described variations. It is similar to the type VII variant which has an incidence of 1%, in which accessory right and left hepatic arteries arise from SMA and

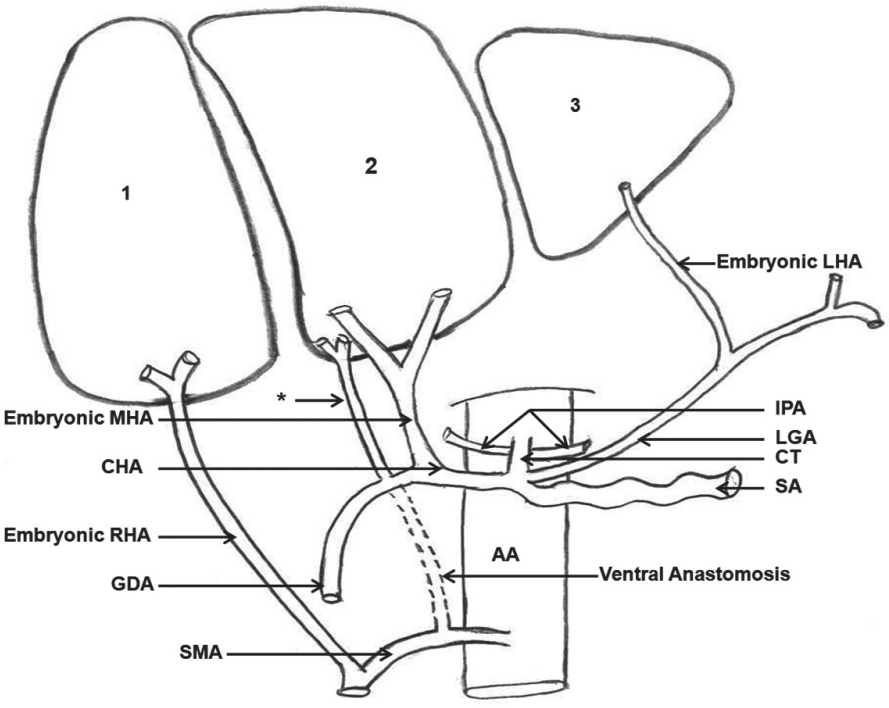

Fig. 4 Diagrammatic representation of the blood supply of the liver. 1, 2 and 3 are the right lateral, central and left lateral lobes of the developing liver. Note the embryonic right hepatic artery (RHA) is a branch of superior mesenteric artery (SMA), middle hepatic artery (MHA), a branch from the junction of common hepatic artery (CHA) and gastroduodenal artery (GDA) and left hepatic artery (LHA) a branch of left gastric artery (LGA). Superimposed are the ventral anastomosis between branches of celiac trunk (CT) and SMA, which may have persisted in this case as accessory right hepatic artery 1 (aRHA1) (*) to supply the liver. AA – abdominal aorta, SA – splenic artery, IPA – inferior phrenic artery.

LGA respectively. However there is no mention of an aRHA from GDA in any of the variations described by Michel (2). A computed tomography study of CT was done by Osman et al, which revealed the classical trifurcation of CT in 63.8% cases (8). In present case, the CT trifurcated classically into LGA, SA and CHA however it also gave origin to both IPA which has been reported by other authors (1).

The mean distance between GDA and pylorus is usually 2.8 cm with a range of 1–5 cm. In the present case the GDA was 4 cm superior to the pylorus hence a high rising artery. Additionally it was coursing anterior to the mid and distal portion of the CBD. Such a course variation is extremely rare as reported by Prudhomme et al. (9). However this is of significance as injury to GDA during laproscopic / open CBD exploration for impacted choledocholithiasis could result in severe haemorrhaging. The GDA could also get injured inadvertently during extension of choledochotomy or while repairing the choledochotomy, getting included in suture bite. The posterior wall of first part of duodenum is the most common site of duodenal ulcer and haemorrhage in these cases is reported to occur in 15–25% cases. The GDA because of its location is the most commonly involved artery. Haemostasis of the bleeding artery and ulcer involves suture ligating the involved artery. The attempt to suture or ligate in the present case can potentially risk injury to underlying CBD. The close relationship between the GDA and CBD although seen rarely, necessitates that before ligation the surgeon verifies the position of the duct either by on table cholangiography, cholecystocopy or by inserting a probe in the duct (9). Lopez-Andujar et al. in 2007 reported concomitant existence of aLHA from LGA and aRHA from SMA with associated presence of LHA and RHA from PHA in only 0.6% cases. In none of the 12 variants reported by them did they find an accessory branch from GDA (3). aRHA1 originating from GDA is another rare though reported finding present in this case. Futara et al. observed such accessory vessel in only 1–2% cases (10). The presence of this vessel at the point where GDA sprouts and turns from its parent CHA could further complicate the retrograde introduction of catheter into the PHA since the PHA and aRHA1 are originating in close proximity to each other and the length of PHA is unusually short. The presence of other accessory hepatic arteries like aRHA2 and aLHA as in present case may lead to inadequate perfusion of the liver parenchyma with chemotherapeutic drugs.

When aberrant arteries are encountered intraoperatively or are not recognized promptly, there is a higher risk of vascular injury. Commonly the aRHA arise from SMA both during cadaveric dissection and intraoperatively with an incidence of 11–26.5% (11). Pancreaticoduodenectomy is the procedure of choice in patients with pancreatic or periampullary tumour and hence the presence of aberrant or replaced aRHA increase the rate of morbidity (11). An aRHA may leads to an alteration in the surgical approach and can also adversely affect the outcomes of the surgical procedure. Excessive handling of these vessels intraoperatively further damages the adventitia of the vessels predisposing to increase risk of pseudoaneurysm (12, 13). Unnecessary retraction of the pancreatic head should also be avoided in such instances as it increases the chances of thrombosis of the aberrant vessels.

During liver transplantation, it is extremely important to understand the complete anatomy and possible variations of liver. Arterial reconstruction is an important step during transplant surgeries. To obtain an optimal perfusion of the graft all the accessory arteries should be recognised at the time of organ collection and reconstructed as insufficient blood supply can lead to graft loss (14). Hepatic artery variations can increase postoperative morbidity, such as bleeding, ischemia or stenosis of the biliary anastomosis, hepatic abscess and hepatic infarction (15).

CONCLUSION

The anatomical variations in the celiac axis and hepatic artery are numerous. This case report identifies the variation in both. The unique findings of this case are the simultaneous existence of accessory branches from LGA, GDA and SMA. The accessory branch from GDA is rare finding. Through knowledge of these arterial pattern are of immense importance in preoperative planning, all surgical and interventional radiological procedures involving upper abdomen as well as hepatobiliary surgeries.

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Vulvo-Perineal and Perianal Paget Disease. Radical Excision and Reconstruction with Singapore Flap

Theodoros Panoskaltsis[1], Theofanis Panagiotis Arkoumanis[2,*], Nikolaos Panagopoulos[1], Dimitrios Mastorakos[2]

ABSTRACT

Extramammary Paget disease (EMPD) is an uncommon intraepithelial malignancy, affecting the vulvo-perineal and perianal region, occurring in 6.5% of all Paget diseases. Usually, an underlying invasive adenocarcinoma denotes a more aggressive behaviour of the disease. We present the multidisciplinary approach in a 75-year old patient with this rare disease. The patient underwent a radical surgical excision and, subsequently, a Singapore flap was used for primary closure. The final histology confirmed the presence of a non-invasive Paget tumor, but a focus of high-grade invasive adenocarcinoma was noted in a perineal nodule. The histological margins were free of tumor. The patient did not undergo any adjuvant treatment because of severe chronic medical problems, although, eighteen months after treatment, she remains well, with no signs of recurrence. In conclusion, radical surgical excision, often necessitating reconstruction techniques, remains the gold standard of care and further adjuvant treatment should be individualised.

KEYWORDS

vulvo-perineal and perianal paget disease; Singapore flap

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INTRODUCTION

In 1901, twenty-seven years after the original paper by Paget on this rare breast tumor, a French Dermatologist, Dubreuilh described the first case of Paget disease in the vulva (1). A few years earlier, in 1893, the first case of perianal Paget disease was reported (2). Extra-mammary Paget disease accounts for 10% of all cases and its estimated incidence is 0.7/100,000 persons/year (3, 4). It affects more women than men and, in the majority of cases; it involves the vulva (85%). Less than two hundred cases of Paget disease affecting the perianal area have been reported in the literature. When it is located in the vulvar and perineal area, invasive foci of adenocarcinoma may be found in 20–79% of cases. An invasive vulvar adenocarcinoma has been reported in 5–18% of cases (5, 6).

The disease in the vulvar and perineal area appears as thickened, erythematous and, often, ulcerative plaques of tissue, with no distinct borders. Under the microscope, a congregation of, mucin producing, intraepithelial neoplastic cells are evident. The pathogenesis of extramammary Paget disease remains unclear and three different theories have been proposed. The first theory suggests that Paget cells originate from mammary-like glands in the the interlabial sulci (7). The second theory suggests that they originate from multipotent stem cells in apocrine glands, found in the epidermal basal layer or infundibular stem cells of the hair follicles (8). The latest theory claims that the so-called Toker cells, with a single round nucleus and usually found in the areola and nipple of the breast, are the origin of extra-mammary Paget disease (9).

The cornerstone of extramammary Paget disease management is the wide local excision with lateral margins extending 2 to 3 cm beyond the affected areas (10). Often, skin or myocutaneous flaps are used for primary surgical closure. However, the disease can reoccur, even with negative surgical margins, especially when an underlying invasive adenocarcinoma is found. In the latter case, a more aggressive treatment is suggested with a concomitant inguino-femoral lymphadenectomy. Different adjuvant therapies have been proposed, i.e. radiotherapy, immuno-modulators, chemotherapy, or even, lately, target therapies, with various degrees of success.

CASE HISTORY

A 75-year old female patient presented with an erythematous plaque with white scaling, affecting the whole vulvar area and extending to the whole perineal and perianal area. She was complaining of itching, irritation and burning in the area. In the last five years, she had undergone, elsewhere, three wide local excisions of different areas of the vulva and perineum. The first local excision took place in 2007, nine years earlier.

CLINICAL EXAMINATION

Neither the clitoris nor the labia were identified. Physical examination was very painful and, except for the erythematous plaques and scaling, several skin erosions were identified, especially, in the perianal area (Figure 1). On physical examination, no palpable inguino-femoral lymph nodes, nor hepato-splenomegaly were identified. On colposcopy, the disease seemed not to extend to the vaginal canal and the Papanicolaou test was negative. The patient underwent anoscopy and rectosigmoidoscopy, where no intraluminar lesions were identified, except for a solid nodule at the perianal area. The anal squamo-columnar junction appeared normal. Also, cystoscopy was normal, although the lesion seemed to affect the opening of the urethra. A computed tomography with intravenous radio-opaque material showed thickening of the vulvar area and perineum, but no enlarged inguino-femoral and pelvic lymph nodes.

The two previous wide local excisions had shown non-invasive Paget disease of the vulva with positive margins and, in the last one, the presence of invasive disease and two foci of underlying adenocarcinoma, up to a depth of 3.5 mm. Positive margins for non-invasive Paget disease were found, even, in the last wide local excision. No lymphadenectomy was performed in any of the previous surgeries. The patient suffered from ischaemic cardiac disease and hypertension, for which she was under close observation and treatment by her cardiologist.

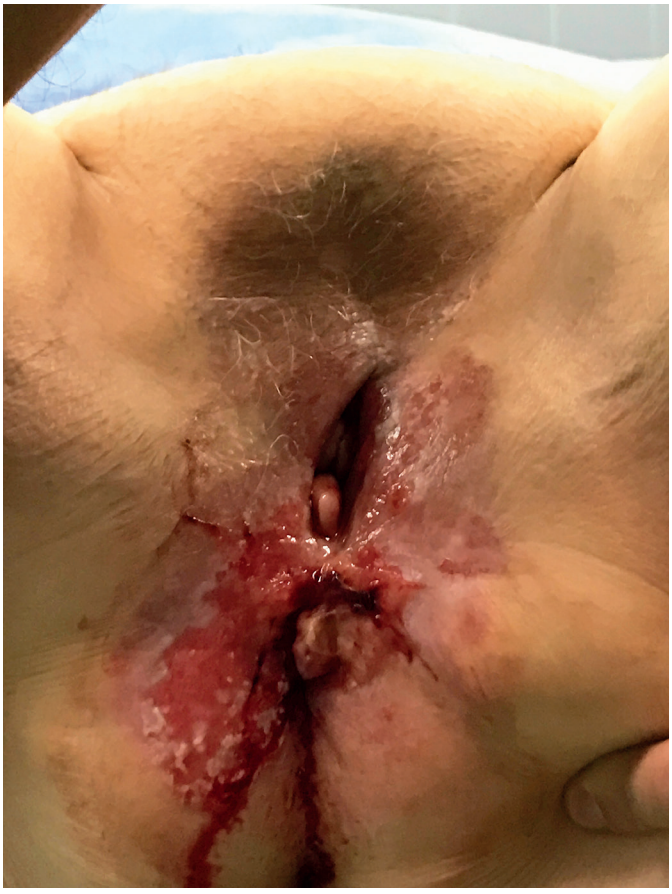

Fig. 1 Extent of disease before final surgery.

Also, in the past, she had undergone a triple cardiac bypass operation.

SURGICAL APPROACH & PATHOLOGICAL FINDINGS

In view of the above, and the negative CT findings for nodal disease, she was scheduled for a radical local excision of the lesion and reconstruction with no regional lymphadenectomy. In the operating theatre, a wide radical excision was performed, in order to include all visible lesions, with a 2 cm margin of healthy tissue. For this reason, the outer 1.5 cm of the urethra were mobilized and cut. The whole mons pubical area was mobilized and the transverse perineal muscles were exposed, along with the external anal sphincter. The whole lateral skin up to the underlying muscles and vaginal canal were mobilized (Figure 2).

Frozen sections confirmed the negative margins of excision, but the perineal nodule was reported as positive for high-grade adenocarcinoma. A further excision at the entrance of the anal canal confirmed the negative margins. Following mobilization of the adjacent skin and vagina, the pubic and the right lateral defects were closed on primary intention. For the closure of the left side, a Singapore flap was used. The flap was centered over the medial thigh crease. The flap measured 13 × 5 cm, with the long axis positioned parallel to the medial thigh crease. The flaps were elevated in an anterior-to-posterior direction and included the deep fascia of the thigh adductor muscles. A posterior incision was extended through the skin and subcutaneous tissue to create an island flap, which was rotated approximately 90 degrees and passed through a tunnel, deep under the skin, lateral to where the labia majora were located in the past. Finally, a negative pressure drain was inserted and the flaps were sutured together to close the defect, with the apex of the flap sutured to the central gluteal area. There was no tension in any of the side of the flap (Figure 3). The blood loss was 200cc and the patient recovered well after the operation. Because of her medical history, she remained under close observation in the Intensive Care Unit. The wound was healing well, but, on the third post-operative day the patient complained of shortness of breath and chest palpitations. An ischaemic cardiac episode was diagnosed and the patient was transferred to the Cardiac Intensive Care Unit for observation. She recovered well, both, from the operation and the cardiac episode. The drain was removed on the 8th post-operative day, but a Foley urinary catherer was left in-situ for a total of 14 days, in view of the urethral cut and shortening. After removal of the Foley catheter, the patient was continent, both, for faeces and urine and the wound, including the flap, healed with no signs of infection, breakdown or haematoma. The patient was discharged from the hospital after 17 days. On final histology, a recurrence of non-invasive

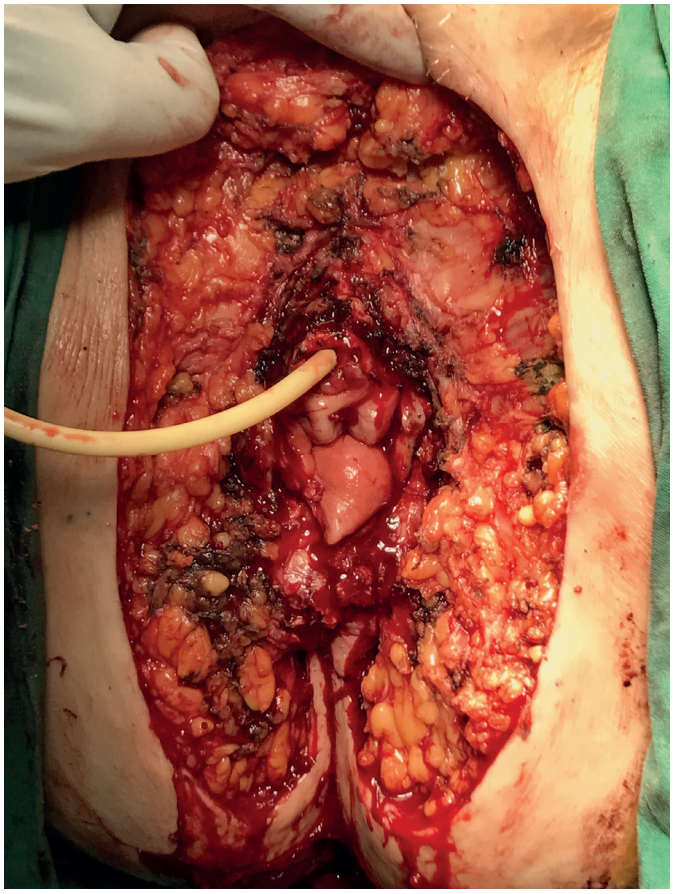

Fig. 2 Operative view after removal of lesion.

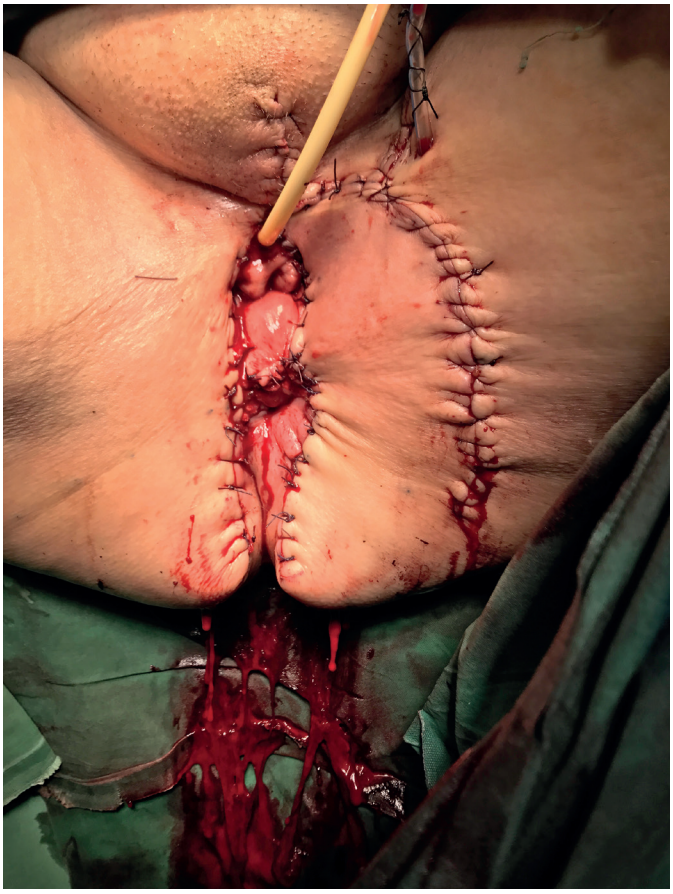

Fig. 3 Primary closure (Singapore flap on left side).

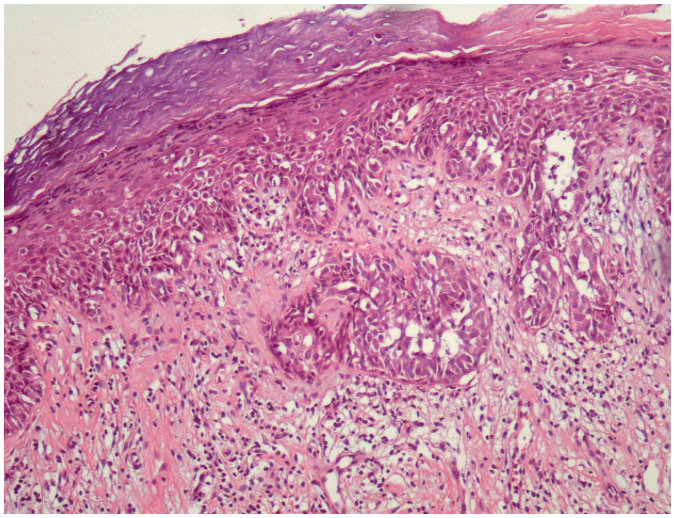

Fig. 4 Hyperkeratotic epidermis involved by Paget cells (H+E ×100).

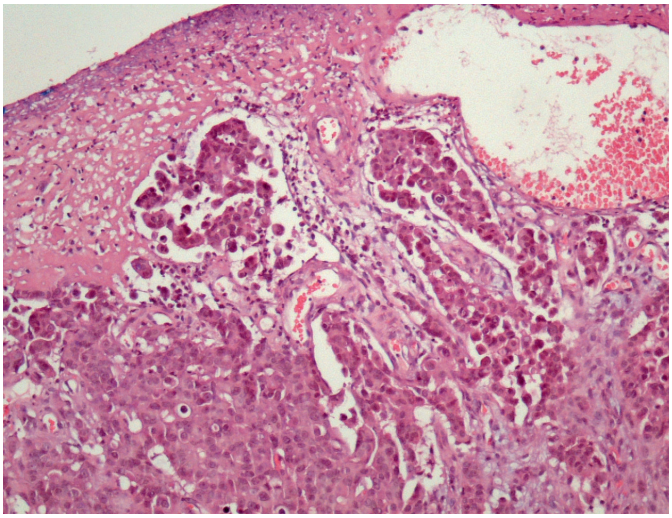

Fig. 5 Ulcerated, infiltrating, poorly differentiated adenocarcinoma (H+E ×200).

Paget disease and a nodule of invasive high-grade adenocarcinoma were confirmed, along with the presence of multiple neoplastic vascular emboli. The disease extended close to the margins on the left lower side of the specimen, although there were many artefacts due to the use of electrocautery.

OUTCOME

Because of her complicated history, only local radiotherapy was proposed as adjuvant treatment. Eighteen months after completion of treatment, the patient remains well, with no signs of recurrence.

DISCUSSION

Extramammary Paget disease is a rare disease, mainly, affecting elderly postmenopausal women. Worldwide, there are only about 200 literature reports of perianal Paget disease. It is estimated that it represents, only, 1% of all malignant tumors in this area and 6.5% of all Paget diseases (4, 5, 10). Based on its aetiological origin, EMPD is classified into primary, as in our patient's case, and secondary types. In the primary type, Paget's disease manifests as a (a) strictly intraepithelial disease, (b) intraepithelial disease with dermal invasion of Paget cells or (c) manifestation of an underlying adenocarcinoma of a skin appendage or subcutaneous gland. In the secondary type, the invasion is secondary to (a) an underlying anorectal adenocarcinoma, (b) an urothelial carcinoma or (c) an adenocarcinoma arising elsewhere (11).The clinical picture of the disease includes an erythematous or eczematous, poorly demarcated, plaque with white scaling and ulcerations. In most of the cases, the most commonly affected area is this of the labia majora, followed by the labia minora, clitoris, inguinal folds, the inner thighs and the perineal and perianal region. Conditions such as vulvovaginal candidiasis, eczema, psoriasis, lichen simplex chronicus and vulvar intraepithelial neoplasia (VIN) should be considered for the differential diagnosis of the vulvar and perineal Paget Disease (12). A detailed histological examination is of paramount importance in order to schedule the management of these patients. Especially, it is important to identify the presence of a co-existent invasive adenocarcinoma. It is identified in about one in four such patients (24%) and it is associated with a high mortality rate, up to 46%. Further, an underlying invasive adenocarcinoma necessitates more extensive surgery (inguino-femoral lymphadenectomy), which is indicated when there is invasive Paget disease of more than 1 mm in depth. The role of sentinel node biopsy is not yet clearly defined. The desirable free surgical margins range from 1 to 5 cm. After surgical treatment of vulvar Paget disease, reported local recurrence rates vary from 34 to 56%. Reconstructive and plastic surgery may be required in order to close the large skin defects. Radiotherapy, both as primary and adjuvant therapy with invasive adenocarcinoma, has been reported, with doses varying from 40 to 65 Gy. Satisfactory results have been reported, with long-term recurrences of <20%. Also, recent data suggest that a dose of approximately 50Gy could eradicate microscopic disease near positive surgical margins and subclinical lymph node metastases (19, 20). The initial experience with Imiquimod shows impressive results in eradicating not only vulvar recurring disease, but, also, disease in the inguinal area. Further results are awaited, as regular, long treatment may produce severe side effects and discontinuation of it (18). Several chemotherapy regimes have been used, mainly for metastatic disease in extra- mammary Paget disease, with various degrees of clinical response. Currently, chemotherapy is, mainly, reserved for distant metastases and palliative treatment (21). Recently, chemotherapeutic agents, in combination with Trastuzumab (Herceptin), have been used for treating metastatic disease with success (22).

In summary, the invasive vulvo-perineal Paget disease requires aggressive surgery, involving radical removal of the vulva and perineum, along with an inguino-femoral lymphadenectomy. As the disease mainly affects women of

advanced age, completeness of treatment may be compromised by several co-morbidities. Even so, local radiotherapy appears to be effective in eradicating microscopic local and lymph node disease. Currently, chemotherapy serves, mainly, as a palliative treatment modality for distant metastases, although its use in combination with Herceptin needs further investigation. Recently, Imiquimod, has produced impressive results in local and metastatic disease and further trials are underway.

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Late-Onset Hypertrophic Pyloric Stenosis in a 14-Weeks-Old Full Term Male Infant

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ABSTRACT

Background: Hypertrophic pyloric stenosis is the most common cause of gastric outlet obstruction in infants, and classically presents at 2 to 6 weeks of age. Delayed presentation is an extremely rare occurrence after early infancy.

Case report: A 14-weeks-old full term male infant presented with non-bilious vomiting, dehydration and hypocloremic metabolic alkalosis. Abdominal ultrasonography revealed tubular mass 20 mm in lenght. Because of unusual age, diagnosis was confirmed with upper gastrointestinal contrast study. Laparoscopic pyloromyotomy was performed. After surgery the child was free of symptoms, had gained weight, and was tolerating a regular diet.

Message: Despite the age hypertrophic pyloric stenosis should be kept in mind in any child who presents with non-bilious vomiting.

KEYWORDS

hypertrophic pyloric stenosis; children; infants; late presentation; non-bilious vomiting

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INTRODUCTION

Hypertrophic pyloric stenosis is a common infantile disorder with an incidence of 1.5 to 4 per 1000 live births. The disease classically presents at 2 to 6 weeks of age often in a previously healthy infant, with peak onset at week 4 (1). It is more common in males than females and in infants born preterm as compared with those born at term (1, 2).

Despite more than a century pass after first successful treatment of this condition, its etiology still remains incompletely understood. Infants typically present with projectile vomiting associated with symptoms of failure to thrive and metabolic alkalosis. An olive-like mass palpable in the right upper abdominal quadrant is being reported less frequently because of earlier diagnosis by ultrasound. Nowadays hypertrophic pyloric stenosis is generally corrected through laparoscopic pyloromyotomy (3).

CASE REPORT

A 14-weeks-old full term male infant presented to our hospital with history of non-bilious vomiting. The child occasionally had vomited non-bilious content for about 20 days. There was no history of abdominal pain, visible abdominal tumor, abdominal distension or melena. One week prior to hospitalization he started to vomit more frequently, and last days he vomited after every meal and it became progressive and projectile. Before admission there was admixture of blood in vomit. On physical examination mild dehidration was found. His vital signs were within normal limits. He had no abdominal distension. Abdomen was soft and non-tender. There was a small vague swelling palpable in the right hypochondrium. Hypochloremic metabolic alkalosis was found. Other biochemical and hematological tests were within normal limits. On ultrasonography a tubular mass measuring 7.5 mm in thickness and 26 mm in length was found. Although child has typical clinical presentation and although he met sonographic criteria for hypertrophic pyloric stenosis, because of unusual age, upper gastrointestinal contrast study was performed. Contrast study reveals a distended stomach with shouldering and string sign with no passage of the contrast from stomach to the duodenum (Fig. 1A). After resuscitation and correction of water and electrolytes disturbances the patient was transferred to pediatric surgeon. Laparoscopy was performed through three 3-mm ports. The pylorus was extremely hypertrophied and firm (Fig. 1B). Laparoscopic pyloromyotomy was done, and the mucosa was seen to pout out nicely. Oral intake was initiated few hours after surgery and the patient was discharged in the third postoperative day without complications. At follow-up, the child was free of symptoms, had gained weight, and was tolerating a regular diet.

DISCUSSION

Hypertrophic pyloric stenosis is typically a disease of 2- to 6-week-old infants with progressive, non-bilious vomiting; its peak occurrence is at 3–5 weeks of age (1–3).

In the case described here, the patient showed feeding difficulty very late, and feeding intolerance worsened. He presented with non-bilious vomiting at 14th week of life, which is very uncommon age for hypertrophic pyloric stenosis. This delayed presentation with unawareness of the hypertrophic pyloric stenosis lead to delayed diagnosis. In the beginning, although he had typical symptoms, gastroenteritis or gastroesophageal reflux was suspected. After diagnostic procedures diagnosis of pyloric stenosis was established and confirmed at the surgery. Although the exact etiology is still unknown, pyloric muscle thickening does not start before birth. The muscle thickening starts

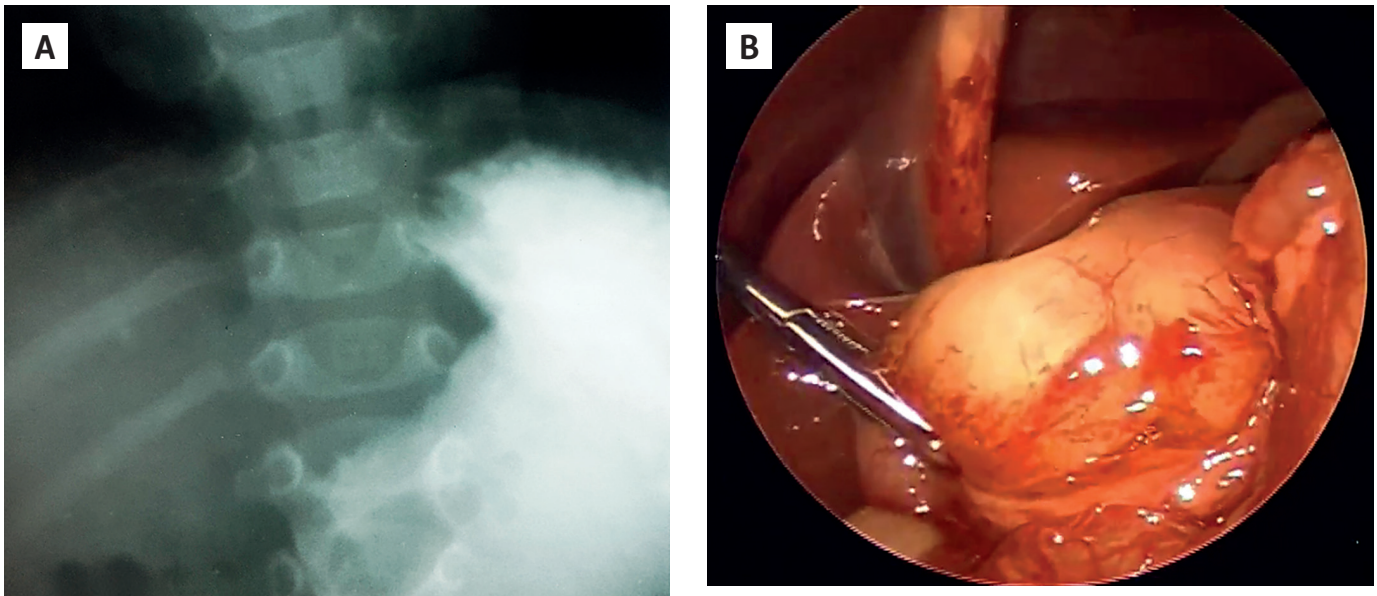

Fig. 1 Hypertrophic pyloric stenosis in a 14-weeks-old male infant. A) Contrast study revealing a distended stomach with no passage of contrast to the duodenum; B) Intraoperative finding on laparoscopy – hypertrophied pylorus.

after birth and the degree of muscle hypertrophy will determine the age of onset of the vomiting (4). In literature there are just few case reports where delayed presentation after typical age was reported, with age range from 5 months to 5 years (4–8). Late onset presentation gives the condition an acquired origin rather than congenital one. Despite the age hypertrophic pyloric stenosis should be kept in mind in any child who presents with non-bilious vomiting.

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