Review Article

# CHIARI FROMMEL SYNDROME – AN EXHAUSTIVE REVIEW

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**ABSTRACT**

A rare endocrine disorder, an orphan disease, described by a German surgeon, Chiari Johann Baptist, and Frommel Richard Julius Ernst, a German gynecologist is Chiari-Frommel syndrome. It affects the women (usually young, 17-35 years) who have recently given birth, suffer from galactorrhea, anovulation, and amenorrhea, continuing for an abnormal period of time, uterus atrophy, and is better known as Chiari-Frommel syndrome in which hyperprolactinemia, eosinophillic hyperfunction is observed. But still its physiopathology remains unclear. The main targets of the disorder are those who are poorly nourished and complaint of lactation, lassitude, headaches, abdominal discomfort, mental distress, depression, breast enlargement, decreased size of uterus and cervix, weight gain, fatigue. Different findings reported are lot of variation but usually normal 17 ketosteroid excretion, atrophied endometrium, hypoestrogenic vaginal mucosa, normal glucose and insulin tolerance test, normal basal temperature curve. Related medications are cortef, eulexin, biperiden. Other drugs tried are tri-p-anisyl chloroethylene (TACE) with methyl testosterone, levodopa, bromoergocryptine, gamma amino butyric acid. Case reports have been also mentioned in the review.

**Keywords:** Galactorrhea, anovulation, amenorrhea, hyperprolactinemia, uterus atrophy.

## INTRODUCTION

Chiari-Frommel Syndrome can be defined as a rare endocrine disorder that affects women who have recently given birth (postpartum) and is characterized by the over-production of breast milk (galactorrhea), lack of ovulation (anovulation), and the absence of regular menstrual periods (amenorrhea) which continues for an abnormal length of time. These symptoms persist long (for more than six months) after childbirth. Due to the absence of normal hormonal cycles, the reduced size of the uterus (atrophy) may occur. Some cases of Chiari-Frommel Syndrome resolve completely without treatment (spontaneously), and hormone levels and reproductive functions return to normal, whereas others require a complete treatment. In this syndrome, hyperprolactinemia is observed.

**Hyperprolactinemia** (**HP**) is the presence of abnormally-high levels of prolactin in the blood. Normal levels are less than 500 ml U/L for women and less than 450 ml U/L for men. The Chiari frommel Syndrome is generally known by different names such as Frommel Chiari, Lactation-Uterus Atrophy, Postpartum Galactorrhea-Amenorrhea Syndrome. Other disorders related to the syndrome are Ahumada-del Castillo Syndrome, Forbes-Albright Syndrome etc.

Forbes-Albright Syndrome is one of the groups of rare endocrine disorders characterized by abnormally high levels of the hormone prolactin due to a tumor of the pituitary gland. Symptoms include the production and secretion of milk from the breasts (lactation) without associated childbirth or nursing (galactorrhea), and the absence of a regular menstrual period (amenorrhea). Women with Forbes-Albright Syndrome generally have breasts and nipples of normal size and appearance, but the pattern of body hair and sexual drive may be reduced. Ahumada-del Castillo Syndrome is a rare endocrine disorder characterized by the abnormal function of the hypothalamus and pituitary glands affecting the secretion of hormones. This disorder affects only women and is not related to pregnancy. The two major symptoms of this disorder include the production and expression of milk from the breasts not associated with childbirth or nursing, and the lack of regular menstruation. There is normal development of secondary sexual characteristics.

Still the physiopathology of this syndrome is not clear. It is believed by Argonz and Del Castillo that the disorder is due to an "eosinophillic hyper function of the anterior lobe of pituitary with increased production of prolactin." It is also to be highlighted that –Forbes et al agree to this but offer the alternate theory that-the pituitary dysfunction may be due to the interference with a pituitary hormone that normally inhibits lactation. Apart from the original studies, 17 additional cases have been reported[1-10]. All the complaints of galactorrhea and amennorhea, usually occur postpartum, whose duration varies from 1-8 years. Condition of some patients improves due to the administration of chorionic gonadotropin or estrogen-progesterone therapy. Presence of chromophobe tumor has also been proved in some cases.

## HISTORY

In 1832, Chiari described the occurrence of amenorrhea, lactation and puerperal uteroovarian atrophy in normal postpartum women and believed that it was due to uterine atrophy. Then in 1855 chiari described it as a

clinical syndrome. In 1882, the syndrome was descriptively studied by Frommel[11, 12].

Chiari, Johann Baptist was a German surgeon. With his two colleagues he did a work on clinical obstetrics and gynecology which was published in 1855 after Chiari's death. He wrote on diseases of the uterus and made his early observations on uterus atrophy.

Frommel Richard Julius Ernst was a German gynecologist. In 1882 Frommel published his description of uterus atrophy due to prolonged lactation. Because of Chiari's earlier contribution, the disorder is now known as the Chiari-Frommel syndrome.

## CLINICAL PICTURE

The patients of this syndrome are usually young women (17-35 years) and are poorly nourished. They seek help due to persistent lactation, lassitude, headaches, and abdominal discomfort. Many are found to be distressed, mentally depressed, especially if prolonged hormone therapy fails to relieve the galactorrhea and initiate menstrual function. Physical findings seen are breast enlargement, free lactation, usually a definite decrease in the size of the uterus and cervix is seen. It is also seen that the vagina becomes dry. Atrophy of uterus is also frequently observed. Weight gain is usually experienced and fatigue becomes progressive. Additional findings are atrophic endometrial, hypoestrogenic vaginal mucosa and a lowered FSH excretion. The 17 ketosteroid excretion shows a lot of variation but is usually normal. The glucose tolerance test and the insulin tolerance test are usually found normal. The basal temperature curve is found to be normal[13].

## SYMPTOMS

Chiari-Frommel Syndrome is a rare disorder characterized by galactorrhea, amenorrhea, and anovulation for more than 6 months after childbirth. These symptoms occur even though the mother is not nursing the baby. The pregnancy which precedes the onset of Chiari-Frommel Syndrome is usually normal, and childbirth and initial lactation are uneventful. However, normal menstrual periods and ovulation do not resume, and persistent discharge from the nipples occurs, which can sometimes last for years. The other symptoms are persistent nipple discharge, emotion labiality, headache, backache, abdominal pain, vision impairment, high prolactin level, low urinary estrogen level, low urinary gonadotropin level, anxiety, and occasionally obesity. Women who have Chiari-Frommel Syndrome for a long time may also have a loss of muscle tone in the uterus and diminished uterine size (atrophy)[14-23].

## CAUSES

Endometrial hyperplasia, endogenous estrogen excess e.g., obesity, tumor, exogenous estrogen, DUB a diagnosis of exclusion (usually not cyclic, occurs irregularly throughout the menstrual cycle), polycystic ovarian syndrome, hypo- or hyperthyroidism, endometrial atrophy, caused by long-term progestin or oral contraceptive use, anatomic or structural lesions, uterine fibroids, foreign body (often intrauterine device), cervical or uterine polyps, pelvic infection (cervicitis, pelvic inflammatory disease), hypothalamic lesion, hyperprolactinemia, Medications (e.g., exogenous estrogen, phenothiazines, reserpine), coagulation disorders, platelet dysfunction, thrombocytopenia, leukemia, medications (e.g. Aspirin, NSAIDs), Clotting factor abnormality: Von Willebrand's disease, hemophilia, hepatic or renal disease, anticoagulant use, complications of pregnancy, spontaneous abortion (miscarriage), ectopic pregnancy, placenta previa, placental abruption, endometrial cancer, risk factors include older age, chronic anovulation, obesity, hypertension, DM, and unopposed estrogen, Systemic disease (e.g., HIV, hepatic disease, renal disease), nonuterine bleeding, vaginal (tear, trauma, or cancer),Cervical (trauma or cancer), urinary (UTI or cancer), rectal (bleeding, trauma, fissure, or cancer),other malignancy (ovarian or uterine tumor, sarcoma),endometrioma[24-25].

## DYSFUNCTION UTERINE BLEEDING

DUB (Dysfunction uterine bleeding) usually results from an imbalance (in postpubertal teenagers), and anovulation (in women in their late 30s or early 40s in the hormonal-endometrial relationship, where persistent and unopposed stimulation of the endometrium by estrogen occurs. Disorders that cause sustained high estrogen levels are polycystic ovary syndrome, obesity, immaturity of the hypothalamic-pituitary-ovarian mechanism.

In most cases of DUB, the endometrium shows no pathologic changes. However, in chronic unopposed estrogen stimulation (as from a hormone-producing ovarian tumor), the endometrium may show hyperplastic or malignant changes. DUB occurs in 20% of adolescent and in 40% of women older than age 40.

Our present knowledge of Hyperprolactinemia as a cause of galactorrhea and menstrual irregularities has its origin in the early 1970's. The observations date back to the mid 19$^{th}$ century and points to these associations as mentioned by Blackwell[26], the development of a specific radioimmunoassay for measurement of human prolactin (PRL)[27] it has been already suggested that in all the three syndromes (chiarri-frommel syndrome, ahumada Castillo syndrome, forbes Albright syndrome), the PRL concentration is elevated.

## CASE REPORTS

**Case 1**

A 31 year old Negro female, in February 1955, complained of postpartum amenorrhea and galactorrhea of 7 years duration and complained of 55 pounds weight gain, since parturition, recurrent left sided headaches, and increased fatigue and malaise. On May 7, 1948, she had a normal delivery of an apparently healthy 9 pound male infant. Physical examination was negative-no gross visual impairment, funduscopic examination showed

slight A-V nicking, and breasts were symmetrically enlarged but not engorged or tender and had no masses. White, thick, milky secretion could be seen from the nipples. A small, freely palpable uterus was revealed on biannual pelvic examination.

**Case 2**

A 19 year old white female had a forceps delivery of a healthy male infant on January 12, 1953. It was an uneventful pregnancy except for gain in weight of 41 pounds and the occurrence of galactorrhea during the third trimester. Although she was not nursing her baby but she continued to have lactation and amenorrhea until the time. She also made complaints of severe incapacitating right sided headaches, often associated with nausea, vomiting. Tiredness and malaise and denied any visual disturbances in vision. Milk secretion was slowed down and withdrawal periods were induced due to cyclic estrogen-progesterone medication. She was also administered chorionic gonadotropin (18 injections of 2000 u .each), but of no help. Physical examination revealed a white female weighing 152 pounds with normal distribution of body hair, no gross impairment of visual fields, and normal funduscopic examination. Her neck was full, but no definite thyroid enlargement could be palpated, chest and heart was normal. Breasts were symmetrically enlarged without any masses and were not tender or engorged. Thick, white, milky secretion could be easily expressed from nipples. Pelvic examination was not remarkable[28].

**Case 3**

A white 31 year old lady delivered a normal female child. Physical examination results were normal. Results of initial physical examination were normal, pregnancy, labor, delivery, immediate puerperium were uneventful and normal. She was given a regular course of estrogen (TACE 25 mg t.i.d for 4 days). First 6 weeks post partum results were normal. Another course of hormone was given due to continued lactation. After 4 months post partum, profused lactation with engorgement of the breasts. Still the patient was amennorhic, although the patient received 2 additional courses of estrogens, 1 course of androgens, and 3 daily 25-mg injections of testosterone. On august 26, 1954, the patient returned due to persistent lactation and continued amenorrhea. Failure was seen even if a combined estrogen-progesterone compound was given to initiate menses. Daily dose of estrogen-androgen was also given for 2 weeks without improvement. Again the patient was seen on dec 2 -1954, at 10 months post partum, at which time lactation was less but persistent. In the month of September, she had a slight bloody vaginal discharge of 2 days, followed by complete amenorrhea.[15] months after delivery, on May 19, 1955, heavy lactation continued daily. Repeated courses showed no results. The patient became depressed and complained of lassitude and weight loss. Sedatives were also given as additional courses. Until June 25, 1957, the patient was not seen again, lactation had ceased and normal menses returned in June 1956-2.5 years after delivery. The patient delivered her second child on April 14, 1958, without any complication of pregnancy or labor or puerperium. Lactation ceased postpartum, the menses returned and the genital tract was examined as normal. Her course was completely normal the next year. At no time the patient presented headache, visual disturbances, or other evidence of a pituitary tumor, and complete recovery occurred without surgery and subsequently pregnancy occurred, so this case should be classified as a true Chiari-Frommel syndrome.

**Case 4**

15 patients with galactorrhea-amenorrhea syndrome were studied before, during and after treatment with bromocriptine. After pregnancy, six had the onset of galactorrhea and amenorrhea and fulfilled the Chiari Frommel syndrome criteria. Four had demonstrable pituitary tumors and thought to have forbes-albright syndrome. They had been previously treated with radiotherapy, but amenorrhea and galactorrhea existed.

Five had the onset of galactorrhea and amenorrhea after oral contraceptive discontinuation and thus considered as ‘post pill’galactorrhea-amenorrhea. Patients were having galactorrhea and amenorrhea from 2 to 16 years. In three patients, administration of levodopa had been unsuccessful in relieving galactorrhea or inducing ovulation[13].

## DIFFERENTIAL DIAGNOSIS

Laboratory study and clinical course differentiates the disease in two cases, i.e.-patients with pituitary tumor and that of the postpartum group. Normal visual fields, absence of headache, spontaneous non surgical recovery, and negative sella turcica x-ray findings are the main distinguishing features in the latter. A; lowered FSH excretion, a usual finding of lowered thyroid function, and positive x-ray evidence of a pituitary tumor are the differential findings in the tumor group. The recovery of the patients of the tumor group occurs only after the tumor has been removed surgically. No subsequent pregnancies have been reported in this group. In three postpartum patients without tumor subsequent pregnancies have been reported. In case of clinical conditions like acromegaly, encephalitis, and early menopause following hysterectomy or oophororectomy abnormal and execessive lactation may occur[29]. Careful study of these patients should pose no difficulty in differentiating the true chiari-frommel syndrome from these conditions.

## TREATMENT

Related medications are cortef (is basically a hydrocortisone in a class of drugs called steroids and prevents the release of substances in the body that causes inflammation), eulexin or flutamide (an antiandrogen and works in the body to prevent the actions of androgens also used in the treatment of

prostate cancer) and biperiden (which may cause drowsiness and is an antiparkinson agent of anticholinergic type). Standard therapy includes the administration of drug bromocriptine (help to reduce prolactin levels, when these levels are reduced, normal ovulation cycles may be restored along with regular menstrual periods). If the symptoms persist for a long period of time, affected individuals can be monitored (CT scan or MRI) for the presence of a pituitary tumor). If a tumor is discovered, it may be difficult to treat if it is very small. Larger tumors can be surgically removed. Greenblatt has stated that almost every conceivable type of treatment has been used in the syndrome and have failed to achieve any consistent results. Therapy includes the use of estrogens, progestins, estrogen-progestin combinations, androgens, thyroid, chorionic gonadotropin and x-ray. Although Greenblatt attempted to restore a normal hormonal balance by corticoid therapy, but he could not detect any significant improvement in any of his patients. TACE (tri-p-anisyl chloroethylene) with androgen (methyl testosterone) has also been used. The prevention of surgical menopausal symptoms following total hysterectomy and bilateral salpingo-oophorectomy are its major indication. Few patients with diverse indications like menopausal syndrome, infertility, chiari frommel syndrome, ovulation inhibition in endometriosis, diminished libido, and senescent vaginitis were also treated from the department of gynecology, Harvard medical school, Boston, and the free hospital for women, Brookline, mass.

Levodopa is one of the agents that may suppress pituitary prolactin[30]. But unfortunately it has not been uniformly effective in patients with galactorrhea-amenorrhea syndrome[31]. Bromoergocryptine, an, an ergot derivative, 2-bromo-alpha-ergocryptine, code name CB-154 showed to inhibit pituitary-prolactin release from lactotroph cells of the pituitary, has anti galactic activity in experimental animals, and also found to suppress post partum lactation[32-34]. Studies conducted in Europe have shown effectiveness of this compound in patients with galactorrhea-amenorrhea syndrome and was introduced in the early seventies[35-38]. But still it is not clear that if the suppressive effect of it on prolactin hypersecretion is permanent or after the discontinuation of the drug hyperprolactinemia may return as revealed in some studies[39-42].

Evidence suggests that gamma-amino butyric acid (GABA), in addition to dopamine functions as a prolactin inhibitor. It also appears that PRL inhibitory activity of dopamine is far greater than that of GABA. Experimental observations in several species, including humans, indicate thatTRH, vasoactive intestinal peptide, cholecystokinin and angiotension II may be involved in the control of secretion of PRL[43]. The physician Dodart, in 1676 described the cessation of lactation related to ergot[44]. The search for an ergot derivative for this purpose with minimal or no ergotoxic effects started in 1960's.In animals, many alkaloids were found to be effective but none could prove useful for humans due to their severe side effects. Other ergot derivatives such as lisuride, meterogoline, and pergolide mesylate were used but had same action as Bromocriptine and cause similar adverse reactions[45-46]. CV 205-502 is a new long acting, non-ergot dopamine agonist which effectively inhibits the secretion of PRL in healthy volunteers[47].

## CONCLUSION

Chiari Frommel syndrome is basically an endocrine disorder affecting the women's of 17-35 ages who have recently delivered a baby. It is a rare disorder which occurs due to absence of normal hormonal cycles. Most of the cases require a specific therapy to for which a few number of drugs are available. The disorder is mainly due to increased production of prolactin. Many cases of its occurrence have been already reported. The literature survey revealed that the Chiari Frommel syndrome is reported to occur in few patients. If the percentage of its occurrence increases further, then it will no longer remain an orphan disease, rather it will become a common disorder. Many drugs have been already screened and some have proved beneficial in treatment as well but yet more and more effective drugs can be expected in the future, so that the disorder can be eradicated completely.

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