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Association of clubbing and hypertrophic osteoarthropathy with ulcerative colitis and regional ileitis

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THE ASSOCIATION OF CLUBBING AND HYPERTROPHIC OSTEOARTHROPATHY WITH ULCERATIVE COLITIS AND REGIONAL ILEITIS

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To the Thesis Committee:

Mr. McGowan has searched for these case records and assembled information which is not available anywhere else in the literature. He was selected by the Refresher Course Committee to represent the senior class on the Post-Graduate Assembly on March 30, 1955.

Very truly yours,

Robert L. Grissom, M.D.,
Assistant Chairman,
Department of Internal Medicine.

RLG:jo

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Introduction

In view of the recent interest in clubbing of the fingers, this study was undertaken to determine the significance of finger clubbing in chronic ulcerative colitis and regional ileitis.

The English and American literature on clubbing in general, and specifically clubbing associated with ulcerative colitis and regional ileitis, has been extensively reviewed and a summary of these findings will be presented. Eighty-two cases of ulcerative colitis and regional ileitis at the University of Nebraska and the Omaha Veterans Administration Hospitals have been reviewed and the results are correlated later in the paper.

History

Clubbed fingers were first described by Hippocrates in 500 B.C. associated with a case of empyema. In the year 1832, Pigeaux (1) wrote of the malady associated chiefly with pulmonary tuberculosis. Von Bamberger (2) and Pierre Marie (3), working independently, described hypertrophic osteoarthropathy as an advanced stage of clubbing in 1889 and 1890 respectively. Since that time there have been well over four hundred articles published on this interesting and controversial subject.(4)

Finger clubbing is synonymous with watch glass nails, parrot-beak nails, drumstick fingers, serpents head or clock pendulum fingers, Hippocratic fingers, essential dactylomegaly and hypertrophic acrodactylopathy to mention only a few. (5)

The bone changes associated with clubbed fingers, presently known as hypertrophic osteoarthropathy, have had numerous names such as the Marie-Bamberger syndrome, periostitis, generalized osteophytosis, secondary osteoarthropathy, and pachyperiostosis. (5)

Pierre Marie in 1890 defined hypertrophic osteoarthropathy as: "Symmetrical osteitis of the four limbs, chiefly localized to the phalanges and terminal epiphyses of the long bones of the forearm and leg, sometimes extending to the roots of the limb and flat bones, and accompanied by a dorsal kyphosis and some affection of the joints." (6) The dorsal kyphosis is not generally mentioned as a part of the syndrome and is not necessary in the definition.

Clubbing is best defined as a painless, soft-tissue proliferation about the terminal phalanges. It is the opinion of most authors that the clubbing and the bone changes are both manifestations of the same process and that the clubbing generally preceeds the bone changes

in order of appearance. Bone changes may or may not be evident dependent on the duration of the clubbing (4).

Classification

For the sake of convenience, clubbing will be discussed under three major categories. These are secondary bilateral clubbing, hereditary bilateral clubbing, and unilateral and unidigital clubbing.

Secondary bilateral clubbing is the enlargement of the terminal segments of all the fingers and/or toes. Causes for this form of clubbing are numerous and only a few of the major causes will be mentioned.

The most common causes of clubbing associated with pulmonary pathology are chronic diseases such as bronchiectasis (7), lung abscess (8), and empyema (9). However, any disease process producing a chronic pneumonitis may be the stimulus for the production of clubbing and/or hypertrophic osteoarthropathy. Clubbing with pulmonary tuberculosis, when seen, is usually associated with cases of long duration.

It is rarely seen in the acute lung diseases such as lobar or bronchial pneumonia, passive congestion, or congenital lung cysts (10). Three cases of clubbing associated with cavernous hemangioma of the lung have been noted in the literature (11) (12). Several re-

ports of clubbing secondary to metastatic lung disease have been reported in the recent literature (13) (14). Clubbing is also seen occasionally in patients with tuberculosis of the spine (15). It is interesting to note that clubbing is known to exist in association with polycythemia secondary to lowered oxygen tensions (5).

Clubbing may be associated with any intrathoracic neoplasm regardless of type or location. Various studies have been made to determine the relationship of area of tumor involvement and/or type of tumor to the eventual development of clubbing. However, the only consistent finding was a peripheral location of the tumor mass in thirteen of fourteen cases (16).

Many types of cardiac disease show clubbing of the fingers and/or toes. In subacute bacterial endocarditis finger clubbing may be one of the earliest signs noted. Congenital heart disease with cyanosis is very frequently associated with clubbing of the fingers and/or toes, while congenital heart disease without cyanosis rarely, if ever, gives rise to clubbing. It is not as a rule associated with congestive heart failure unless it is of a very chronic nature (5).

Gastrointestinal disease, involving both liver and

bowel, is frequently the only primary disease that can be discovered in cases that show clubbing. Cirrhosis, especially the cholangiolitic type, is known to have associated clubbing. Disease involving the bowel, primarily the colon, may produce clubbing in a small number of cases. Most diseases associated with chronic diarrhea have shown isolated instances of clubbing. Ulcerative colitis and regional ileitis appear to be the primary gastro-intestinal diseases producing clubbing. (17) (18) (19)

Hereditary bilateral clubbing occurs in otherwise apparently healthy individuals and acts as a Mendelian dominant in genetic transfer. Well documented cases that are apparently hereditary have been reported by several authors (20) (21) (22).

Unilateral clubbing is most generally associated with aneurysm of the arch of the aorta, the innominate, or the subclavian arteries. There are case reports of the occurrence of unilateral clubbing associated with arterio-venous fistula of the brachial artery (16).

Unidigital clubbing is for the most part secondary to trauma that results in damage to the blood vessels and/or nerves in the arm or hand. There are reported cases of hereditary bilateral unidigital clubbing of the thumbs. (5)

Clinical Features

Clubbing is not restricted to any one age group. It has been reported in a child of seven and one-half months (23) and in the aged. The sex distribution of clubbing is dependent on the sex distribution of the primary disease. In the majority of cases the onset of clubbing is insidious, the exception being in those cases where clubbing is secondary to carcinoma of the lung or mediastinum. Clubbing is ordinarily not associated with any unpleasant physical symptoms. However, because of the increased blood flow in these fingers there may be increased warmth, diaphoresis, and tingling, but no actual painful sensation (5).

The most complete and most widely accepted criteria for the diagnosis of clubbed fingers was written by Lovibond (24) in 1938 as follows: "Clubbing is commonly seen first in the thumb and index digit, and spreads to the others later. The process starts at the root of the nail just beyond the interphalangeal joint as a definite, firm, transverse ridge more obvious on the dorsal aspect of the finger. The overlying skin is smooth and shiny, the patient often complaining that the cuticle has begun to grow more rapidly over the nail. A vascular turgescence of the nail

bed in the early stages imparts a lilac hue, and in the well developed clubbed finger a full, rounded, and cyanotic appearance. - - - . As the deformity develops, the base of the nail becomes elevated so that its outline may be discerned beneath the skin. In severe clubbing the nail can be rocked backwards and forewards, giving the impression that it is floating on a soft oedmatous pad. If the clubbing is of long standing, the terminal phalanx may become hyperextended."

Figure 1
1. Normal finger, showing base angle of nail.
2. Curving of nail, a variation of normal.
3. Mild clubbing, base angle obliterated.
4. Gross clubbing, base of nail projects.
5 and 6. Chronic paronychia and Heberdens node, fundamental base angle unaltered.
From Lovibond, Lancet, Feb. 12, 1938.

Definite diagnosis of early clubbing rests upon one salient feature as described by Lovibond. "It is the profile of the nail which is so important, and the angle of that profile is the basic element in correct diagnosis. Normally the angle of the nail with the finger is one hundred and sixty degrees and regardless of deformities of the nail itself, curving, spatulation,

etc., it is solely a disturbance of this angle on which the diagnosis of clubbing, early or late, rests; so the angle must be distorted to greater than one hundred and sixty degrees." (See Figure 1)

Definite diagnosis of clubbing is made when the base angle is distorted to one hundred and eighty degrees or more. Between one hundred and sixty and one hundred and eighty degrees the clubbing is classified as either early or questionable."

In no way does the clubbing associated with gastrointestinal disease differ from clubbing seen in association with other diseases.

Radiographic Findings

The bones most frequently involved in hypertrophic osteoarthropathy are the long bones of the extremities, metacarpals, metatarsals, the proximal phalanges, and in far advanced cases; the clavicles.

The bone changes are characterized by: 1) deposition of subperiosteal new bone along the shafts of the involved bones, and 2) simple burr formation, or later, a resorption of the distal end of the terminal phalanx (17).

Symptomatic regression of hypertrophic osteoarthropathy is the rule after the primary cause is removed,

but only rarely does the regression show radiographically (16) (25) (26).

Pathology

The pathologic findings in clubbed fingers are solely those of edema and soft-tissue swelling. The majority of this swelling is located between the nail-bed and the bone. In advanced cases there may be a pressure atrophy of the terminal phalanx (27).

In the long bones the pathological findings are essentially these: 1) initial thickening of the periosteum with diffuse infiltration of round cells and polymorphonuclears; 2) division of the periosteum into two layers with invasion by fibrillar material which later becomes osseous. Shortly after deposition the new bone fuses with the original cortical surface. In some cases, the joint spaces may be invaded by round cells with resultant thickening of the synovial membrane. Advanced cases may show erosion of the articular surface and narrowing of the joint space (15) (28) (29).

Etiology

There are five prominent theories at the present time. Each has its merits but none seem adaptable to all the required situations. These theories are: 1)

toxic absorbtion with subsequent subperiosteal irritation; 2) dysfunction of the pituitary gland; 3) decrease in oxygen tension of the blood; 4) reduced surface area of the red cell; 5) and chronic increased blood flow with increased periosteal nutrition (30).

The theory of toxic absorbtion with subsequent subperiosteal irritation was held for many years because of the high incidence of clubbing in suppurative chest diseases. Recent work by Ray and Fisher (16) showed the following: One hundred and thirty-nine cases of bronchogenic carcinoma were studied histologically to determine whether infection played a part in the development of osteoarthropathy and/or clubbing. Infection was clinically obvious in fifty-seven cases, large abscesses were present in three, and in two the carcinoma was in a lung cyst. However, in none of these cases was clubbing or osteoarthropathy present.

Pituitary dysfunction is cited by many examiners as the cause of the production of clubbing and the osteoarthropathy. They support their theory by the fact that many of these patients show gynecomastia clinically, and at autopsy reveal involvement of the pituitary, especially in cases of carcinoma of the lung (30).

Mauer (31) incorporated the remaining theories into a reasonable and workable hypothesis. Clubbing occurs when there is arterial anoxia due to congenital or acquired lesions, or residence at high altitude. However it also occurs in many diseases in which the erythrocyte sedimentation rate is rapid and the arterial oxygen saturation normal. In these latter cases the vascular bed is wide, blood flow is rapid, and the tissue is warmer than normal. Rapid sedimentation rates, with intravascular rouleaux formation, interferes with tissue oxygenation by decreasing the diffusion surface per unit of hemoglobin.

Mauer also suggests, that with escape of rouleaux through the arterio-venous anastomoses, so numerous in the fingers and toes, rapid blood flow and high levels of arterial and venous oxygen saturation may be present simultaneously with a resultant low oxygen tension in the digital tissues.

Charr and Swenson (7) have demonstrated that the local vascular bed is increased and widened in cases of clubbing. This has been confirmed by Mendlowitz and Wilson (32) working independently. These investigators have found increased peripheral blood flow, and this, plus the reluctance of the erythrocytes to release

their oxygen, leads to arteriolar anoxia, low tissue oxygen tension, and clubbing. This theory would provide the same mechanism for clubbing in chronic infections, neoplasms, or metabolic defects leading to abnormal fibrinogen and globulin levels, as in the classical cases of arteriolar anoxia.

The most rapidly evolving and the most severe types of osteoarthropathy are seen in cases of mediastinal and lung tumor where the sedimentation rates are rapid and arterial anoxia is present. Here the two types of anoxia may act synergistically (31).

Other disease processes show increased sedimentation rates and arterial anoxia, but not clubbing. This may be explained by the fact that in these cases the blood flow and tissue temperatures are low in the tips of the extremities, whereas it has been proposed that increased blood flow and increased temperature, plus tissue anoxia are needed for the development of clubbing.

There have been many attempts to produce clubbing by artificial methods in experimental animals, but for the most part these have been unsuccessful. Temple and Jaspin (33) cite the following experimental methods: 1) Von Bamberger placed material from a human lung ab-

scess into the rectum of rabbits but could produce no clubbing; 2) Phemister used intravenous injections of various organisms without success; 3) Harter and Churchill tied off the bronchi in cats and monkeys but could get no results; 4) Mendlowitz and Leslie anastomosed the left pulmonary artery to the left auricular appendage in four dogs and produced hypertrophic osteoarthropathy in only one; 5) Compere, Adams, and Compere (34) injected paraffin into the lungs of dogs and produced lung abscesses but no clubbing.

The etiology of clubbing and hypertrophic osteoarthropathy in association with gastro-intestinal disease is not evident, and the few reported cases make determination of the etiology even more difficult.

Schlicke and Bargen (18) in 1940 reported seven cases of clubbing in association with ulcerative colitis. Three of the seven also showed an associated terminal ileitis. Duration of symptoms ranged from nine months to ten years with an average of three and one-half years.

Crohn (19) in 1949 reported four cases of clubbing in a series of two hundred and twenty-two cases of regional ileitis. In this same work Crohn reported a series of thirty-six cases of ileo-jejunitis in which he

noted twelve patients with clubbing of the fingers. In twenty-two cases of ileo-colitis, clubbing was noted in only one patient.

Present Study

Because of the limited number of reported cases, eighty-two cases of ulcerative colitis and regional ileitis were reviewed. The cases were obtained from the University of Nebraska Hospital and the Omaha Veterans Administration Hospital.

Approximately 90% of the eighty-two cases were recorded as ulcerative colitis. One of the eighty-two had a diagnosis of both ulcerative colitis and regional ileitis. An exact breakdown of these figures is not given because of inaccuracies in coding.

Clubbing of the fingers was noted in eight cases, for an incidence of 9.8%. As many of the cases were rather incomplete, especially in regard to physical description of the fingers, the true incidence may be higher than 9.8%.

The salient features of the historical findings of the eight patients with clubbing of the fingers are summarized in Table 1. Of these, seven were males and one was female. The ages ranged from fourteen to seventy-two with an average age of twenty-nine. The duration

of symptoms ranged from three months to eight years. Anorexia was complained of by all patients, and was described as marked in three. Diarrhea, defined arbitrarily as three or more stools per day, was noted

Case Number	Sex, Age, and Race	Duration of Symptoms	Anorexia	Diarrhea >3 Stool per day	Constipation	Alternating Diarrhea and Constipation	Weight Loss	Clubbing	Chills	Present Status
C.B. UNH	M 72 W	2-3 yrs.	+	+ 2 mos	-	+ 2 years	30-40 lbs.	+	+	D.
I.F. UNH	F 12 W	28 mos.	+++	+ 28 mo.	-	-	12 lbs.	+	-	U.
G.C. UNH	M 21 W	8 yrs.	+++	+ 2 mos.	-	+ 8 years	30 lbs.	+	+	U.
N.S. UNH	M 19 W	1 yr.	++	+ 1 yr.	-	-	59 lbs.	+	+	I.
J.B. UNH	M 14 W	3 mos.	+++	+ 3 mos.	-	-	24 lbs.	+	+	I.
J.K. VAH	M 33 W	2 yrs.	++	+ 3 mos.	-	+ 2 years	32 lbs.	+	-	U.
R.H. VAH	M 33 W	2-3 yrs.	++	-	+ 2-3 yrs.	-	Unk.	+	-	U.
L.S. VAH	M 29 W	5 yrs.	++	+ 2 yrs.	-	+ 3 years	30 lbs.	+	+	U.

Table 1. Summary of Histories.

in seven of the eight patients. However, four of the eight, at some time during the course of the disease, complained of alternating diarrhea and constipation.

Five of the eight complained of chills. The present status of five patients is unknown. Two are improved, and one is dead.

The pertinent clinical features are summarized in

Case No.	Diagnosis		Procto-scopic		Temperature		Associated Diseases	Manage-ment	
	Clin-ical	Radio-logy	Nor-mal	Abnor-mal	<100	>100		Med-ical	Surg ical
C.B. UNH	U.C.	U.C.	-	+	-	+	Bronchopneu. Thrombosis Sup.Mes. Art	+	-
I.F. UNH	U.C.	U.C. & T.I.	-	+	+	-	None	+	-
G.C. UNH	U.C.	Unsat.	-	+	-	+	None	+	-
N.S. UNH	T.I.	T.I.	+	-	-	+	None	+	-
J.B. UNH	U.C.	U.C.	-	+	-	+	None	+	-
J.K. VAH	U.C.	U.C.	-	+	+	-	None	+	+
R.H. VAH	R.I.	R.I.	+	-	+	-	None	+	-
L.S. VAH	R.I.	R.I.	+	-	-	+	None	+	-

Table 2. Clinical Data.

Table 2. The clinical diagnosis was ulcerative colitis in five patients and regional or terminal ileitis in the remaining three. These findings were confirmed by

radiographic study in all but two cases. In one (G.C.), the barium enema was unsatisfactory because of the patients inability to retain the barium. In the second case (I.F.), both ulcerative colitis and regional ile-

Case No:	Hemoglobin		W.B.C.	E.S.R.	T.S.P.		A.G. Ratio		St. occult blood	Stool for O. & P.	Long-Bone x-rays	Chest X-ray
	<10 gram	>10 gram	>10,000		Nor.	Abnor.	Nor.	Abnor.				
C.B. UNH	+	-	-	None Done	-	-	-	-	+	-	None Done	Neg.
I.F. UNH	-	+	-	None Done	-	-	-	-	+	-	None Done	Neg.
G.C. UNH	-	+	+	None Done	-	-	-	-	+	-	None Done	Neg.
N.S. UNH	-	+	-	34	+	-	-	+	+	-	None Done	Neg.
J.B. UNH	-	+	+	34	+	-	-	+	+	-	None Done	Neg.
J.K. VAH	-	+	+	48	+	-	+	-	+	-	+	Neg.
R.H. VAH	-	+	+	31	+	-	+	-	+	-	+	Neg.
L.S. VAH	-	+	+	43	-	+	-	+	+	-	++	Neg.

Table 3. Laboratory Data.

itis were apparent by roentgen study. Of these eight patients, five showed frequent temperature elevations above one hundred degrees Fahrenheit during their hos-

pital course. The proctoscopic examination showed hyperemia, contraction, and ulceration in all five patients who had ulcerqerative colitis. The three patients with regional ileitis exhibited no proctoscopic findings. No associated disease which might account for clubbing, was present in seven of the eight patients. The other patient (C.B.), was found to have bronchopneumonia and a thrombosis of the superior mesenteric artery at postmortem examination. In this case, a chest film on admission was negative. The bronchopneumonia developed terminally and was probably of only several days duration. All eight patients were treated by medical management, and one of the eight also had surgical treatment for his disease.

The important laboratory findings in these eight patients are summarized in Table 3. All of the cases with clubbing showed a hypochromic anemia. The hemoglobin ranged from 9 to 13 grams/100 cc, with three of the patients showing a value less than 10.2 grams. The red blood count ranged from 3.62 to 5.04 million/cmm, and seven of the eight patients had an erythrocyte count of 4.0 million/cmm, or more. A leukocytosis was noted in five cases. An erythrocyte sedimentation rate was recorded in only five of the eight cases and in all of these it was greater than 30 mm/hour. Total serum

protein determinations were recorded in five cases; only one of which showed a value below 6.0 grams/100 cc. Of these five, three showed a reversal of the albumin-globulin ratio. Stool studies were recorded in all cases, and all were negative for ova, parasites, and pathogens. All were positive for occult blood. Long-bone x-ray studies were done in only three of the eight patients, and all three showed radiographic evidence of osteoarthropathy. Chest x-rays on admission were negative in all cases.

Case History

Three of the case histories of patients showing clubbing of the fingers will be presented for the sake of clarity.

Case 1. N.S. was a 19 year old white male whose chief complaint was diarrhea. He had from three to four stools per day for a period of one year, associated with a moderate degree of anorexia and a weight loss of fifty-nine pounds. The barium enema was negative, but the small bowel series showed spasm of the duodenum and terminal ileum. The proctoscopic examination was normal. He had frequent temperature elevations greater than one hundred degrees Fahrenheit. Laboratory findings are as follows: hemoglobin was

13.2 grams/100 cc; 4.5 million red blood cells/cmm; erythrocyte sedimentation rate of 34 mm/hour; white blood count of 8,300/cmm with a normal differential; T.S.P. of 6.84 grams/100 cc with 3.54 grams albumin and 3.30 grams globulin; stools negative for ova, parasites, and pathogens. No long-bone x-ray studies were done, but finger clubbing was clinically evident. The chest x-ray was negative for disease.

Case 2. J.B. was a 14 year old white male whose chief complaint was bloody diarrhea, consisting of five to seven stools per day, for three months. He experienced marked anorexia during this period, coincident with a weight loss of twenty-four pounds. The barium enema revealed a severe ulcerative colitis, and this was confirmed by proctoscopy. The mucosa was edematous and congested, and showed numerous ulcerative lesions. The temperature was frequently elevated above one hundred degrees Fahrenheit during hospitalization. Laboratory findings are as follows: hemoglobin 12.2 grams/100 cc; 4.62 million red blood cells/cmm; white blood count 11,800/cmm with a marked left shift; erythrocyte sedimentation rate of 34 mm/hour; T.S.P. of 6.50 grams/100 cc with 2.78 grams albumin and 3.72 grams globulin; stools were negative for ova, parasites, and

pathogens. No long-bone x-ray studies were done, but finger clubbing was clinically evident. The chest x-ray was negative for disease.

Case 3. L.S. was a 29 year old white male whose disease began five years prior to admission with diarrhea without blood. This progressed to bloody diarrhea of eight stools per day about three years later. He experienced moderate anorexia for one year prior to admission coincident with a weight loss of thirty pounds. The barium enema was negative, but the small bowel series showed regional ileitis. The proctoscopic examination revealed no abnormalities. Laboratory work on admission showed: hemoglobin 10.15 grams/100 cc; 5.0 million red blood cells/cmm; white blood count of 4,700 per cmm with a normal differential; the erythrocyte sedimentation rate was 43 mm/hour; T.S.P. was 4.30 grams per 100 cc with 1.95 grams albumin and 2.35 grams globulin; stools were negative for ova, parasites, and pathogens. The chest x-ray was negative for disease and long-bone x-rays showed advanced hypertrophic osteoarthropathy. Clubbing was clinically evident.

Discussion

From the preceeding, it can be seen that the history, clinical and laboratory findings in the eight cases which

presented clubbing, did not differ appreciably from the usual features of ulcerative colitis and regional ileitis without clubbing. There was no evidence that any other disease process, especially cardiovascular or pulmonary, might account for the clubbing. The presence of hypochromic anemia in all, and an elevated erythrocyte sedimentation rate in those in whom this procedure was done, were rather consistent findings. However, both are a usual feature of ulcerative colitis and regional ileitis.

These findings would tend to substantiate Mauer's theories regarding etiology. However, in this series, the incompleteness of the studies done in this regard, makes it impossible to draw any conclusions.

Summary and Conclusions

1) The literature regarding clubbing and hypertrophic osteoarthropathy has been reviewed generally, and specifically in relation to ulcerative colitis and regional ileitis.

2) In the eighty-two cases reviewed, eight patients clinically evidenced clubbing and three showed hypertrophic osteoarthropathy roentgenographically. No other cause for the clubbing or osteoarthropathy was evident.

3) No particular feature of these two diseases

served to distinguish those cases in which clubbing occurred and those in which it did not.

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