Original research

Does the change in clubbing marks the course of DPLD: The result of a pilot observation.

Parthasarathi Bhattacharyya[1], Rantu Paul[2], Saikat Nag[1], Dipanjan Saha[3]
[1]Consultant, [2]Research assistant, [3]Research fellow, Institute of Pulmocare and Research, Kolkata

Abstract

Background: Clubbing is a common association of DPLD from different causes. There could be a relationship of the activity of DPLD with that of the degree of clubbing. Thus, it may be worthwhile to see the change in clubbing with the course of DPLD.

Methods: Patients of DPLD being diagnosed on clinico-radiological (HRCT) basis were evaluated with spirometry for measurement of FVC (forced vital capacity), 6MWT (six minutes walk test), and serial measurement of clubbing with the help of a modified shadow-gram at the beginning and once on follow up after treatment. The change in the FVC and 6MWT were charted and calculated with that of the measurement of the different variables of clubbing as profile angle, hyponychial angle, and the ratio between the distal and proximal interphalangeal diameters.

Results: Out of 17 patients of DPLD observed in such fashion, 11 had improvement and 6 had deterioration in both the FVC (forced vital capacity) and the 6MWT. This changes was noted significant in both the parameters for improvement (P=0.04 and 0.01 respectively) and for FVC alone (P= 0.001) for deterioration. Though not statistically significant, there has been a parallel change in all the parameters of clubbing both in the improvement and the worsening group.

Inference: The change in clubbing appears to mark the course of a DPLD patient. The observation needs further validation

Running title: Clubbing may mark the course of DPLD

Key Word : Clubbing DPLD, IPF hyponychial angle, profile angle, interphalangeal diameter

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ABBREVIATION:

DPLD: Diffuse Paranchymal Lung Disease

FVC: Force Volume Capacity

SGRQ: Saint George's Respiratory Questionnaire

6MWT: 6 Minute Walk Test

IPF: Idiopathic Pulmonary Fibrosis

PDGF: Platelet Derived Growth Factor

HGF: Hepatocyte Growth Factor

DID: Distal Interphalangeal Depth

PID: Proximal Interphalangeal Depth

6MWD: 6 Minute Walk Distance

HRCT: High resolution computerized tomography

Corresponding author:

Dr. Parthasarathi Bhattacharyya
Institute of Pulmocare and Research
DG-8, Action Area-1, New Town, Kolkata- 700156

INTRODUCTION:

Clubbing, the bulbar deformity of the finger and toe-tips (1). It is commonly observed in patients of diffuse parenchymal lung diseases (DPLD) (2) although its importance in the condition is not yet clearly defined. We measured the clubbing objectively in a group of patients of DPLD on treatment longitudinally in more than one occasion along with the measurement of other standard parameters as FVC and 6MWT. Further attempt was made to see whether the change in clubbing has any relation to that of FVC, and 6MWT. Here, we present the findings of our observation done in a real world practice.

METHOD:

The patients of DPLD (diagnosed on clinicoradiological basis with help of HRCT chest) of various etiologies presenting to our OPD with clubbing were randomly chosen for the measurement of

clubbing. They were evaluated as per the real world practice style of the practicing pulmonologist that included the documentation of spirometric variable as FVC and 6 minutes walk test. Alongside, the clubbing of the left index finger of the patients were measured with a modified shadowgram using an indigenously developed instrument been utilized successfully to measure clubbing (3) within 15 days of the measurement of FVC and 6MWD. It allowed making digital photographs of the finger shadows on a simple instrument; the pictures were further used to measure the different angles and depths by using the AUTOCAD 2002 software to assess precisely the degree of clubbing. The profile angle, the hyponychial angle, and the ratio of the distal to the proximal interphalangeal diameters were considered for the assessment of the clubbing. All the measurements of clubbing were accomplished by two independent observers and the average was taken for consideration of analysis. Repeat shadow-grams were done in same patients on at least one follow up occasion for each (following a variable duration of treatment) along with repeat measurement of the FVC and 6 minute walk distance as per the patients' desire and convenience in a real world practice. Finally, the value of the clubbing parameters along with along with that of FVC and the 6MWD measured before and after treatment were charted in two groups according to the response to therapy as group A and group B according to improvement or deterioration in both the FVC, and 6MWT. The change in measurements of these parameters were statistically analyzed using paired Students't' test in both the groups separately.

RESULT:

Out of 17 patients (male: female=11:6, mean age=54.53±8.40) being followed with repeat measurement of the clubbing parameters, FVC, and 6MWT,six showed worsening while eleven patients showed improvement on follow up. The details of them are charted in table 1. The patients of group A (n=11) had shown significant improvement in FVC and 6MWT with associated improvement of clubbing while the patients of group B (those deteriorated; n=6) had shown the reverse with the FVC alone showing significant change (p=0.001). It is interesting to note that the change in clubbing has been parallel to the other established parameters as FVC and 6MWD to note the course of the disease in both the groups.

Criteria	**Group A: Improvement (n=11)** Duration of treatment =276.27± 213.95 *days*			**Group B: No Improvement (n=6)** Duration of treatment =337.5± 224.72 days		
	before treatment Mean ±SD	*after treatment Mean ±SD*	*p value*	*before treatment Mean ±SD*	*after treatment Mean ±SD*	*p value*
FVC	1.94±0.42	2.16±0.60	0.041	1.85±0.45	1.68±0.46	0.001
6 MWT	1366.82 ±254.35	1430 ±250.67	0.01	1333.33±131.59	1315.83±248.66	0.75
Clubbing measurement						
Hyponychial angle	184.91± 10.45	184.77±9.44	0.95	185.92±13.51	185.67±15.63	0.84
Profile angle	164.86±5.63	168.32±4.58	0.09	169.33±5.93	168.00±7.42	0.19
DID/PID	0.92± 0.10	0.88±0.08	0.29	0.96±0.09	0.94± 0.07	0.25

Table 1: shows change in FVC, 6MWT and the value of different parameters of clubbing both in patients with improvement and worsening on treatment ($p<0.05$) has been regarded significant (marked bold).

DISCUSSION:

Clubbing of nails is an important and mandatory observation in general physical examination. It develops from a kind of sponginess of the nail bed out of the thickening of the soft tissue at the nail bed especially beneath the proximal nail plate (1). Clubbing has been observed in variety of conditions that includes neoplastic, cardiovascular, pulmonary, gastrointestinal and other diseases (2). On closer examination, the affected nail-beds of clubbed fingers show loosely textured large primitive-appearing fibroblasts with occasional extravascular infiltration of lymphocytes and eosinophils in a widely meshed reticular network.

In chronic clubbing, an increased deposition of collagen in the nail bed has been observed (5). There have been several hypothesis of the development of clubbing and growth factors (like platelet derived growth factor- PDGF, hepatocyte growth factor-HGF) are implicated to play a mechanistic role through the stimulation of the proliferation of mesenchymal calls, fibroblasts, smooth muscle cells and others (6, 7, 8). Spontaneous regression or even disappearance of clubbing has been documented in several conditions especially after removal/ withdrawal of the inciting factors (9, 10, 11). Therefore clubbing bears the potential to be a marker of the course of a disease state associated with this particular abnormality.

DPLD is a disease of progressive fibrosis of the lungs from varied causes. It is not uncommon in a pulmonologist's practice and more and about 5% of our OPD populations are DPLD patients. (12). Clubbing is a common observation in DPLD with over 50% of the IPF patients (the most widely studied DPLD along with sarcoidosis) having clubbing (2). There has been a good correlation between the smooth muscle proliferation and fibrotic changes in the lungs to that of the degree of clubbing (13). Interestingly, in usual interstitial pneumonia (pathological counterpart of IPF), the smooth muscle proliferation happens to be one of the most important pathological phenomenon (14) and several growth factors including PDGF play a significant role in the pathogenesis of this disease of dysregulated fibrogenesis (15). Hence, an association of the disease activity of UIP can go well with the process of making or resolving clubbing when it is present. Incidentally, to our knowledge, nobody has looked for the change in clubbing with time or with the response to treatment in any DPLD. Thus, this important clinical sign remained a neglected or overlooked entity in relation to the disease assessment in IPF or any other DPLD. This could be partly because of difficulty in objective measurement of clubbing or because of short survival of the most widely studied DPLD as IPF.

Conventionally, clubbing has been measured by shadowgram where the hyponychial angle has been found to be the best discriminator (16); there are other methods too (17, 3). We have used successfully a simple objective method of clubbing measurement developed by us that needed making digital shadowgram and using a measurement software (AUTOCAD 2002) (3). Better and easier objective measurement has been a serious welcome in the field. We have also taken into account the measurement of 6MWT, a marker of functional ability that has been found to be a reliable and valid measure of the disease status and a valid endpoint for clinical trials in IPF (18). We have also compared the clubbing measurement with change in FVC that has again been found to be a reliable and valid measurement for the lung function status in patients with IPF (19). The demonstration of the change in clubbing to go parallel to the changes in 6MWT and FVC suggest that the association is a positively co-related. Incidentally, the change in clubbing has not come statistically significant in any of the groups. However, the result suggests that the change in the degree of clubbing may be a sensitive marker alone with the other used parameters as FVC and 6MWT. Hence, one needs to measure precisely the clubbing in a larger number of patients to establish our claim that clubbing, when present, can reflect the disease activity in IPF / DPLD and that the serial measurement of clubbing can help to understand the course of the disease.

There are several limitations of the study; the most important being the small number of the patients. The methods of assessment should have included the other measurements as the diffusion capacity, quality of life, radiological (HRCT) changes etc. Subgroup analysis of IPF and non-IPF DPLDs could have been better but was not attempted considering the small number of the patients. However, despite the weaknesses, to our mind, the observation appears unique and needs validation with further studies.

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