Journal of Pharmaceutical Research International

33(44A): 219-227, 2021; Article no.JPRI.74160
ISSN: 2456-9119
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

Clinical Features, Diagnosis and Treatment Strategies of Limb Girdle Muscular Dystrophy: An Observational Study from South India

S. Nigama Chandra[1*], A. Anka Rao[1], G. S. N. Koteswara Rao[1], K. Umasankar[1] and A. Rajasekhar Reddy[1]

[1]K L College of Pharmacy, Koneru Lakshmaiah Education Foundation, Vaddeswaram-522502, Guntur, AP, India.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2021/v33i44A32610
Editor(s):
(1) Dr. Rafik Karaman, Al-Quds University, Palestine.
Reviewers:
(1) Yin-Hsiu Chien, National Taiwan University Hospital, Taiwan.
(2) Mohd Izham Mohd Zain, KPJ University College, Malaysia.
Complete Peer review History: https://www.sdiarticle4.com/review-history/74160

Original Research Article

Received 06 August 2021
Accepted 16 September 2021
Published 17 September 2021

ABSTRACT

Objective: The present observational study describes the natural course of clinical features, family history, and diagnosis pattern and treatment strategies in rare genetic disorder, Limb girdle muscular dystrophy (LGMD).
Research Design: Observational study
Methods: Clinically/Immunohistochemically/genetically confirmed LGMD patients diagnosed between February 2019 and March 2021 were ambispectively included. The primary outcomes, secondary outcomes such as clinical presentations, behavioral problems, diagnosis pattern and treatment strategies were studied. A correlation of primary outcomes and steroid, non-steroid regimens were achieved. The demographic data was expressed using descriptive statistics mean ± standard deviation [SD]. The significance level was fixed at $\alpha = 0.05$
Results: 300 LGMD patients were included, out of which 272 patients participated in the study. The mean onset age of symptoms was 8-21 years (13.7 ± 1.9). The mean age of wheelchair bound was found to be between 18 years to 37 years (25.23±1.4) in 123 patients. Bedbound status was attained in 22 patients with a mean age between 18 to 49 years (27.5±2). 7 patients reported death

**Corresponding author: E-mail: nigamac111@gmail.com;*

during the study phase with a mean age of 39.2±2.4 (38-45). Comparatively, both steroid and non-steroid regimens using patients exhibited loss of ambulation at 38 years of age. The disease confirmation reported was primarily by clinical examinations (89%) and genetic testing was of minimal number (22%).

Conclusion: The outcome measures in the large cohort is similar to that of the Western population despite variability in medical prudence. The contemporary observational study adds to the real-world evidence in approaching better research strategies to treat the LGMD community.

Keywords: Steroids vs non-steroids; LGMD; Mutation; inherited; Muscular dystrophy; gene.

1. INTRODUCTION

Limb girdle muscular dystrophy (LGMD) is a rare genetic disorder. The prevalence of LGMD is unknown. However, studies suggest range estimation of LGMD's from 1 in 14,500 to 1 in 123,000. These are clinically identified by difficulty in walking, muscle degeneration, muscle weakness. The symptoms are variable on the specific mutated gene.

Typically, the clinical course of LGMD is variably progressed and is dependent on the severity of the individual genetic mutation [1]. Studies suggest that males or females can act as the asymptomatic carriers [1]. Predominantly, symptoms are presented in teen-age. Initial weakness is observed at the hip and proximal leg muscles. 25 types (such as LGMD1, LGMD2A, LGMD2B, LGMD2C and so on) of LGMD are classified based on the chromosomal loci [2,3]. LGMD ranges from mild to severe forms with onset symptoms in the first decade and eventually a rapid progression [4]. Diagnosis includes the clinical examination of physical symptoms, serological examinations muscle biopsy and genetic testing [5,6]. Serological examinations can identify the levels of Serum creatine kinase. Fiber size variation and fiber hypertrophy, muscle fibers (scatter, regeneration and degeneration) can be identified by Muscle biopsy followed by a biochemical test of proteins for the diagnosis of a specific LGMD. The confirmation can be achieved by genetic testing.

This progressive muscular disorder has no cure to date [7]. However, there is a palliative treatment for LGMD and supportive therapy is available for the progression control. In India, there are no long-term follow-up study to chronicle and describe the natural history, symptoms, diagnostic pattern and its survival pattern of LGMD [8]. The present was as an attempt to study the prevalence and survival and diagnosis pattern of LGMD in a large cohort of the LGMD population from India. In context to this lacuna, we conducted an observational study on LGMD diagnosed patients and compared their prevalence pattern in collaboration with the Amaravati Muscular Dystrophy Association (AMDA) to elucidate the epidemiology, diagnosis criteria and compare steroids and non-steroid regimens in these patient populations of South India.

2. MATERIALS AND METHODS

The study was performed on 300 patients on whom a provisional diagnosis of LGMD was made. The Initial selection included patients who met our criteria and have given informed consent to participate in the study and those patients were examined personally. The Secondary selection included results of clinical examination and review of muscle biopsy specimens. Inclusion criteria were patients of both genders with progressive symmetric limb girdle weakness and with investigations of serum creatinine kinase activity, EMG and muscle biopsy. Patients with LGMD including metabolic and inflammatory myopathies, Dystrophinopathy, spinal muscular atrophies, congenital myopathies were excluded. Exclusion criteria included congenital onset, ptosis or weakness of external ocular muscles, skin complaints, facial weakness, distal muscle involvement more than proximal, presence of florid active denervation, ragged red fibers or cellular infiltrates on muscle biopsy or fat accumulation in muscle fibers, abnormalities within Dystrophin gene Xp21 were included under exclusion criteria.

A tentative subdivision was made into autosomal recessive, sporadic and autosomal dominant cases. Sporadic cases can be autosomal recessive or new mutations of an autosomal dominant form.

2.1 Data Collection and Statistical Analysis

Patients were examined based on standardized protocol and literature review [9]. Neurological

history included questions about the age of onset, initial symptoms of weakness, motor milestones, muscle thinning, muscle twitching, lordosis presentation, family history, behavioral assessments, therapeutic and management practices used, cardiac abnormalities experienced were included in the questionnaire. Breathlessness, fatigue, sleep related symptoms and headache upon waking were clustered under respiratory question. Genetic investigations were observed in this study. Serum Creatinine Kinase activity, muscle biopsy specimens, immuno histochemical analysis of alpha sarco- glycan were included in the study. The demographic data was expressed using descriptive statistics mean ± standard deviation [SD] [10]. Primary outcome is expressed as the number and percentage of patients with age as mean ± SD (range). The data was skewed, median and range are provided. The presenting clinical features at initial evaluation are presented as the number of patients and also indicated in percentage demonstrating individual clinical features.

Data was collected and analyzed in Microsoft (Redmond, WA, USA) Excel 2016 and Graph Pad Prism version 9.1.0. (Graph Pad Software, Inc., San Diego, CA). The significance level was fixed at $\alpha = 0.05$.

3. RESULTS

An agreement from AMDA was obtained in February 2019 to conduct an observational study for the identification and intervention of demographics, clinical parameters and diagnostics ratio and their distribution in South India.

Out of 300 study population, 28 patients were excluded who did not meet primary inclusion criteria. 18 patients were excluded after reviewing muscle biopsy specimen reports. 4 patients were thought to have congenital myopathy, 6 patients had the typical distribution of weakness with distal leg involvement more than proximal muscles. Hence, 272 patients were engaged in our study for further analysis.

The mean age at onset of symptoms was 8-21 years (13.7 ± 1.9); Lordosis and Calf hypertrophy was present in 93.3% of the patient population. Consanguinity was reported in 39%, cervical lordosis was found in 57% population, 69% of the population has shown lumbar lordosis.

Among 272 total patients, 44.8% of patients were wheelchair bound. The mean age at which the patient was wheelchair bound was found to be between 18 years to 37 years (25.23±1.4). The patients who were bedbound 8.5% with a mean age between 18 to 49 years (27.5±2). 7 patients who reported death during the study phase with mean age of 38-45years (Table 1).

A significant effect on older age of presentation, toe walking, delayed mental milestones and respiratory abnormality was reported. These were the significant predicators in bedbound patients. There was no significant effect of cardiac abnormality on the duration of ambulation loss. There were fewer death cases reported and hence due to this, there was no possible correlation analysis made with other groups. So, only descriptive parameters were reported (Table 2).

Behavioral parameters like attention deficit hyperactivity disorder (ADHD) reported in 30% patients, Oppositional defiant disorder (ODD) seen in 20% of patients, post-traumatic stress disorder (PTSD) seen in 20% patients, obsessive- compulsive disorder (OCD) seen in 30 % patients, generalized anxiety disorder in adults (GAD) seen in 30 %, panic disorder seen in 50% patients (Fig. 1).

Physiotherapy was the primary therapy reported in 44% of the patients. Ancient medicine practices such as homeopathy was used by 6% of the population and Ayurveda was used in 8% of the patient population. Acupuncture, which is the oldest Chinese tradition, was reported in 1% of the population. 44% of the population reported steroids usage and only 1% of the population reported stem cell therapy (Fig. 2).

Table 1. Statistical data of the primary outcome measures of 152 limb girdle muscular dystrophy patients in South India

Outcome	*n* (Age in percent)	Mean age (in years)	Mean Current age (in years)
Wheelchair bound	123 (44.8%)	25.23±1.4 (18- 37)	27±4.3 (18-40)
Bedbound	22 (8.5%)	27.5±2 (18- 49)	36±8.5 (18-51)
Death	7 (2.5%)	39.2±2.4 (38-45)	Not applicable

Table 2. Correlation and analysis of clinical parameters with primary outcome measures

Variable Measured	Wheelchair bound mean±SD; (*n*)	Non- wheelchair bound mean±SD; (*n*)	*P*	Bedbound mean±SD; (*n*)	Non- bedbound mean±SD; (*n*)	*P*
Age at onset (years)	13.8±1.9; (123)	13.5±1.8; (149)	0.7	13.1±1.2; (22)	13.7±1.8; (250)	0.96
<18	23[19%] (123)	36[24.1%] (149)		2[9.1%] (22)	54[21.6%] (250)	
18-25	43[35%] (123)	54[36.5%] (149)		7[31.8%] (22)	94[37.6%] (250)	
>25	57[46.5%] (123)	59[39.7%] (149)	0.56	13[59.8%] (22)	102[40.8%] (250)	0.61
Age at presentation (years)	18.5±2.5; (123)	17.4±1.8; (149)	**0.003**	18.1±3.1 (22)	18.0±2.4 (250)	**0.04**
Mile stone delay	67[54.4%] (123)	84[56.3%] (149)	0.68	18[81.8%] (22)	142[56.8%] (250)	0.19
Frequent falls	116[94.3%] (123)	133[89.26%] (149)	0.15	21[95.4%] (22)	229[91.6%] (250)	0.31
Gowers's sign	88[71.5%] (123)	43[17.8%] (149)	**0.001**	19[86.36%] (22)	112[44.8%] (250)	**0.001**
Respiratory abnormality	6[4.8%] (123)	39[26.1%] (149)	**0.001**	0[0%] (1)	29[40.84%] (71)	-
Cardiac abnormality	6[11.7%] (51)	2[2.8%] (69)	0.41	1[12.5%] (8)	11[9.6%] (114)	-
Muscle thinning, Muscle twitching	19[15.4%] (123)	18[12%] (149)	0.48	5[22.7%] (22)	32[12.8%] (250)	0.21
Family history	22[17.8%] (123)	37[24.8%] (149)	0.29	4[18.1%] (22)	56[22.4%] (250)	0.3

**Figure in parenthesis indicate number of patients; value less than 0.05 represent statistically significant*

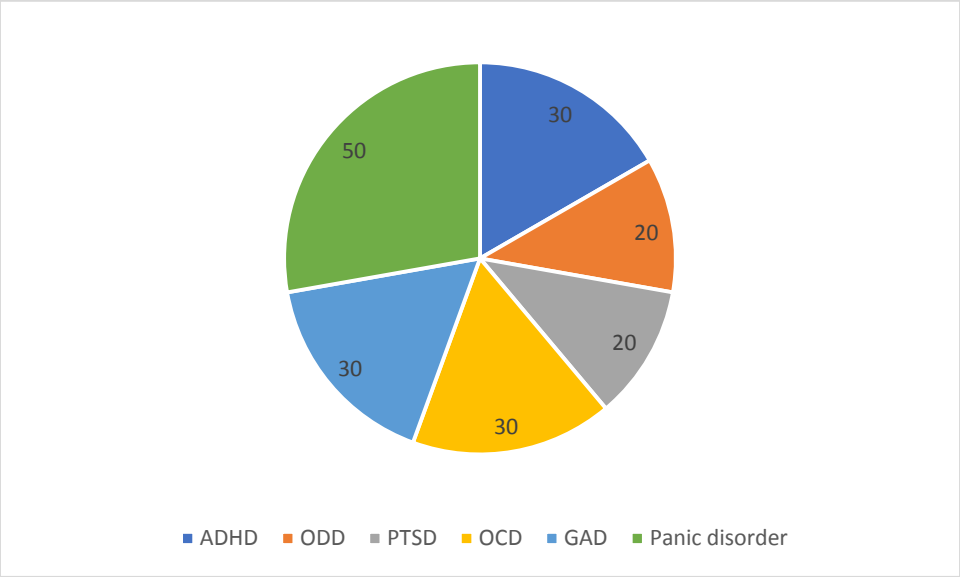

Fig. 1. Behavioral parameter distribution in LGMD

**ADHD= attention deficit hyperactivity disorder; ODD= oppositional defiant disorder; PTSD= post-traumatic stress disorder; OCD= obsessive- compulsive disorder; GAD= generalized anxiety disorder in adults*

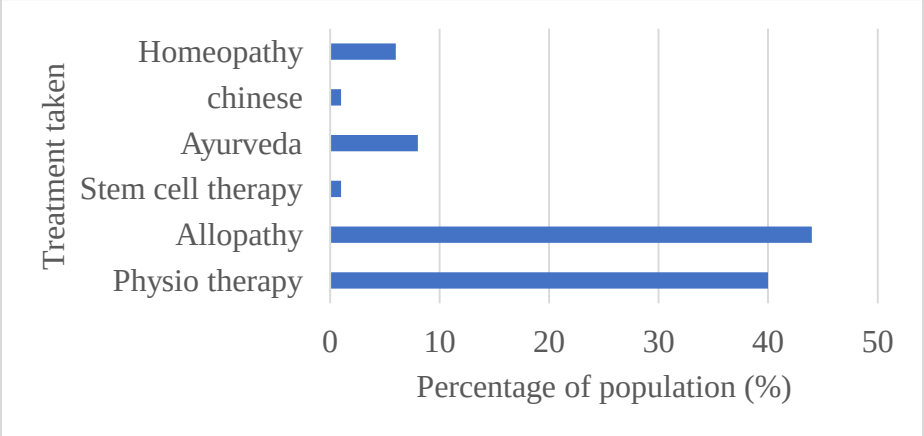

Fig. 2. Treatment strategy LGMD

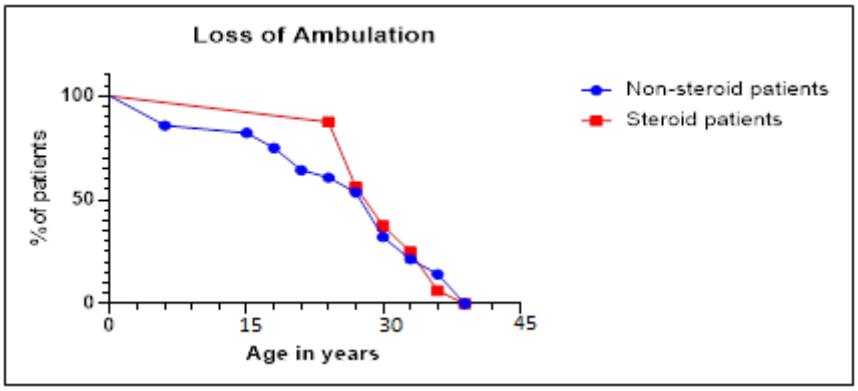

Fig. 3. Steroid vs. non-steroids loss of ambulation

A Kaplan–Meier plot was constructed for loss of ambulation relative to age (years), grouped by steroid patients (n = 90, red line) vs non-steroidal patients (n = 184, blue line). Both regimens using patients demonstrated loss of ambulation at the mean age of 38 years irrespective of the interventions used. However, there is a sudden drop in ambulation of steroidal patients whereas, there was a steady loss of ambulation was observed in non-steroidal patients. In case of non-steroid using patients, onset of ambulatory status distortion started at 7 years with steady rate in loss of ambulation. (Fig. 3).

There was a wide range of variations in the diagnosis pattern reported. Hence, it is reported in descriptive parameters. Clinical examination was reported in 89% of the patients, serological examinations in 21% of the patients, muscle biopsy in 40%, genetic analysis is in 22% of the patients. The autosomal dominant patients were found to be 70% and autosomal recessive is found to be 30% (Table 3).

4. DISCUSSION

There are many studies in LGMD with improper information and reports. This observational study mainly focuses on systematic and depth analysis of clinical interpretation and diagnosis of 300 LGMD population, of which 272 patients fit into the study.

All the known cases of LGMD were included in this study. Initially, 300 patients were included but after comparing with inclusive criteria only 272 patients were fit into the criteria. Those individuals were crosschecked with muscle biopsy specimens and clinical examination. The prevalence was seen in adults more than children. Age at onset is the age of initial identification of difficulty; Age at presentation is the age of clinical symptom identification and attribution of muscle disorder by the physician.

The onset age was between 8-21 years, which is consistent with the other published studies. It was observed that there was a substantial cavity between the onset age of symptoms and diagnosis performed among the patients. This could be attributed to lack of awareness of the disease existence by the parents, or due to diagnostic delay by the primary physicians, especially when the phenotype of the patients is skewed toward language or mental delay [11]. Major muscles involved were pectorals iliopsoas, gluteal muscles, hip adductors and hamstrings. Motor affections such as Weakness of pectoralis, iliopsoas, gluteal, hip adductors, and hamstring muscles were involved. The age of onset of symptoms of lordosis and spinal curvature is when the patient loses the ambulation capacity. The spinal curves progress and include the entire thoracic and lumbar spine with a potentially dangerous increase in the pelvic obliquity in wheelchair bound patients. However, surgery does not have much beneficial effect on life expectancy or reducing the symptoms. When arising from the floor, affected individuals must use hand support to push themselves to the upright position. Proximal muscles are more affected severely. Calf muscle hypertrophy due to replacement of muscle fibers with fat. Para spinal weakness leading to kyphoscoliosis. Mild facial weakness in patients with disease duration of 22 to 27 years. Distal muscles involved are wrist and finger extensors, tibialis anterior and toe extensors.

Weakness started mostly in proximal leg muscles or both upper and lower limbs, frequent falls, raising from a squatting position (Gowers's sign) in most of the patients. Squatting on the floor is the common custom in Indian culture, often identified as the initial motor difficulty presentation. This can be due to the lower strength of hip and thigh muscles. Deterioration of muscle progresses and thereby degenerating muscle movement with an increase of age [12]. Few patients had facial weakness, asymmetric weakness, and elevated serum creatinine kinase activities. The clinical features of different genotypes were not so different. Calf hypertrophy was mostly seen in sporadic and autosomal patients. However, the severity of symptoms was seen in autosomal dominant persons. In addition, poor clinical suspicion of the symptoms by the primary physician was the stumbling block in the majority of the patients. In addition, this leads to the delay in taking adequate care to delay/minimize the symptoms.

LGMD mainly affects between 8-21 years of age. Symptoms like walking difficulty is the early childhood presentation of LGMD. Diet patterns do not suggest the major clinical symptoms. But the symptomatic management by taking a protein diet benefitted patients. Since the progression risk is high, the effect of dietary management is negligible [13].

Among the primary outcome measures, the mean age of wheelchair bound stage was 25 years to 37 years. Despite ethnic variability, LGMD patients lose the ability to walk at a median age of 32 years and often patients lose

walking ability either earlier than 30 years or after 34 years of age.

According to standard studies, consanguinity is the notion in 88%of the study groups. Consanguinity is mainly seen in south Indian culture [14]. LGMD is autosomal dominant or recessive inherited where consanguinity is not a major factor. However, most of the LGMD cases were attributed to consanguine marriages. The concordance of immediate siblings affected with LGMD were young brothers. The clinical picture is assessed based on symptoms of older siblings. Because of this imaginary assessment, few young female siblings also reported LGMD without any genetic confirmation or primary diagnostic pattern. This primary concept of imaginary assessment affected clinical enrollment and management therapy.

Respiratory muscles and cardiac muscles were involved. Progressive muscle weakness results in variation in degree of breathing. However, there is highest respiratory muscle difficulty reported in the non-ambulatory patients. This was attributed to shortness of breath and involuntary trembles. Also, it is understood that heavy breath and palpitations are observed especially in the severe wagered walking stage due to fear of falling. There was also lung dysfunction involvement and cardiac involvement. The cardiac involvement develops as cardiac arrhythmia or cardiomyopathy that leads to cardiac failure.

Deterioration of ambulatory status had an early onset in non-steroidal patients, while steroidal patients had a delay in loss of ambulation. Hence, it was interpreted that the usage of steroids enhances the patients' ambulatory status but in a small ratio.

Physiotherapy and acupuncture therapy has shown a significant improvement among the patients in the study. However, acupuncture has shown lower beneficial results and reported in fewer patients. Reportedly, physiotherapy helped to reduce muscle wasting. Stem cell therapy was reported in 1% of the patients. However, stem cell therapy has not shown any significance in the improvement of muscle strength. Furthermore, side effects such as weight gain, soring pains during nights were observed due to stem cell treatment.

There was a significant improvement in clinical parameters with the usage of steroids (reportedly prednisolone and deflazacort at 0.35 mg/kg and 0.75mg/kg body weight respectively). Deterioration of ambulatory status had an early onset in non-steroid using patients, while patients with steroidal treatment had delayed loss of ambulation which indicates the usage of steroids enhances the patients' ambulatory status. Oral steroids delay the loss of ambulation and probably adds quality years to the life of the patients suffering from DMD while non-steroidal treatment reduces adverse events, change in body weight along with delayed disease progression however with compromised quality of life. A notable improvement was reported in the survival pattern with steroid therapy along with prolongation of the period of ambulation and delay in the attainment of bedbound status by approximately 25 and 36 months, respectively. These findings are similar to those reported in the recent study literature. Chronic cardiac and respiratory abnormalities were the substantial cause of death in 7 patients. However, the principal cause could not be ascertained since either the death is at the local hospital or at home, where the exact reason was not described. Behavioral changes were observed in the patients. Anxiety and panic disorder was reportedly a major outcome of the patients. Patients also have various levels of mental retardation.

Primary diagnosis was reportedly done by clinical assessment and correlating the results which were confirmed by serum creatinine levels. ENMGs and muscle biopsies aid as the secondary Further, it is genetically confirmed to understand the deletions and mutations in the gene. Studies suggest that female act as both asymptomatic and symptomatic carriers of genetic mutations. The percentage of autosomal dominant mutations is found to be highest, further analysis and study is done in future studies [15].

Table 3. Analysis of diagnosis parameters in LGMD patients

Diagnosis	Percentage of population (%)
Clinical examinations	89
Serological examination	21
Muscle biopsy	40
Genetic analysis	22

5. CONCLUSION

In conclusion, this is the first study from South India describing the natural history pattern of LGMD of genetically/immunohistochemically confirmed patients. The patterns of major LGMD milestones, including milestone delays, motor difficulties, onset age, age at loss of ambulation and death. Additionally, this study suggests the pattern of behavioral problems, the diagnostic ratio in the study population. The diagnosis ratio reported is similar to global trends suggesting a lack of proper and accurate diagnosis. Hence, this study highlights the current scenario of obstacles involved in an accurate diagnosis establishment and concordance of LGMD management. Oral steroids delay the loss of ambulation compared to non-steroid patients.

CONSENT

Hereby, the authors certify that we have obtained appropriate patient consent forms. Each patient has given his/her informed consent for her/his clinical information to be reported in the journal. The patients understand that their names will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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families - detection of carrier status in symptomatic and asymptomatic female relatives. Neuromuscul Disord. 2009;19(2):108-112

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle4.com/review-history/74160