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PRELIMINARY STUDY OF L1 SYNDROME PATIENTS WITH MENTAL RETARDATION

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ABSTRACT: L1 syndrome is a hereditary neurological X-linked disorder with a spectrum of phenotypic features such as Mental retardation, X-linked Hydrocephalus, Spastic paraplegia, Aphasia, and Adducted thumbs. The L1 syndrome is caused by the mutations in L1CAM gene. The present study has involved in the identification of the patients with L1 syndrome and comparison of consanguinity with family history. This is the first kind of study from India to know the frequency of phenotypes. Screening of L1 syndrome patients was carried out in various Clinics, Hospitals and Schools run by NGOs in Karnataka. Data were analyzed by using SPSS 20. Totally 113 patients were identified as L1 syndrome patients, and among 113 patients Ten and Seven patients belong to MASA and CRASH family respectively. Of all the L1 syndrome clinical features, Mental retardation and Aphasia has been found to be a very prominent clinical symptom in present data. Nearly 40% of the patients associated with more than four L1 syndrome features. However, the relation of consanguinity and L1 syndrome needs to be investigated. To our knowledge, the present study is first of its kind with larger patient's size of L1 syndrome with widely heterogeneous phenotypes. The occurrence of heterogeneous clinical features of L1 syndrome provides an insight for planning molecular testing both in familial and sporadic cases. We have shown the existence of consanguinity and family history in L1 syndrome patients. Present data revealed that, the prevalence of L1 syndrome is promising and needs to be exploited for screening mutations in patients in Karnataka.

KEYWORDS: L1CAM, L1 Syndrome, Mental retardation, Consanguinity, Aphasia.

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1.INTRODUCTION

L1 syndrome is the hereditary neurological disorder that primarily affects the nervous system. This is due to the mutations in the L1CAM gene and is located near the telomere of the long arm of the X chromosome (Xq28) [1]. This cell adhesion molecule has been implicated in a number of different cellular processes such as neuronal cell migration, myelination, axonal growth and pathfinding [2]. The mutations in this L1CAM gene interrupts the above normal functions, which leads to the development of several neurological defects and abnormal phenotypical characters, such as Hydrocephalus, Mental Retardation, Spastic paraplegia, Adducted thumbs, and Agenesis of corpus callosum. In humans, these defects are overlapping with each other [2, 3]. X – Linked hydrocephalus (XLH) was first described in 1949 [4]. A family with 15 members with sex-linked hydrocephalus as hydrocephalus [5]. One of the earlier studies [7] on a family with X – linked Mental retardation (XLMR) and thumb – flection deformity, reports the mutations in the L1 CAM gene might be a frequent cause of Mental retardation [8, 9], and was supported by the previous study [10], in which 23 families with recessive spastic paraplegia with Mental retardation have been found. All of the above phenotypical conditions such as Mental retardation, Adducted thumbs, Spastic paraplegia, Aphasia were clinically combined together called it MASA syndrome [11]. A family with XLMR reported as having “Complicated spastic paraplegia” [12]. XLH, MASA Syndrome, a form of HSP have been attributed to mutations in the L1CAM gene and their clinical signs overlap [13,14, 15 and 16]. Since the main features of L1 syndrome include Corpus callosum agenesis, Mental retardation, Adducted thumbs, Spastic paraplegia, and Hydrocephalus, which make a condition referred to as CRASH Syndrome [17]. The clinical spectrum of CRASH syndrome is highly variable and may involve any combination of these symptoms [15]. At the severe end, there might be patients with massive hydrocephalus resulting in pre – or perinatal death, whereas at the mild end there are patients with mild Mental retardation as their only abnormality [15]. So, the main features of L1 syndrome include Corpus callosum hypoplasia, Mental retardation, Adducted thumbs, Spastic paraplegia, and Hydrocephalus are highly variable and may involve any combination of these symptoms. In this study, we have tried to identify the L1 patients in few areas of the Karnataka state and assess the spectrum of L1 syndrome more specifically, based on clinical findings.

2. MATERIALS AND METHODS

Study design and population

The present study was approved by an Institutional Ethical Committee of the University, reference number KU/IEC/05-09/2014-15 and Shivamogga Institute of Medical Sciences and Hospital, Shivamogga, Karnataka. Patients were identified with the help of doctors and clinical diagnosis. In order to collect the clinical data, the standardized questionnaire was prepared with the help of clinicians. According to the questionnaire, a detailed family history of the patients was taken and recorded after obtaining written informed consent from the patients. So, we have reviewed the

medical records carefully for the presence of L1 syndrome symptoms and any other physical abnormalities and all of the patients were also examined individually.

Data analysis

Data were analyzed using SPSS 20, segregated the collected data by cross-tabulation and analyzed the phenotypes by using frequency distribution. Correlation of the consanguinity with family history by F-distribution curve was analyzed, obtained data were clearly plotted with graphical representation and Pie chart.

3. RESULTS AND DISCUSSION

In this study, we explained clinical criteria allowing us to score the severity of the phenotype in every patient and every family. Our findings showed Ten and Seven patients belong to MASA and CRASH family respectively (Table 1 and Figure 1).

MASA and CRASH Crosstabulation

Table 1: Cross tabulation and frequency of MASA and CRASH family

		CRASH				Total
No. of Symptoms		1.00	2.00	3.00	4.00	
M	1.00	0	39	7	1	47
A	2.00	1	40	8	0	49
S	3.00	0	17	23	0	40
A	4.00	0	0	4	6	**10**
Total		1	96	42	**7**	146

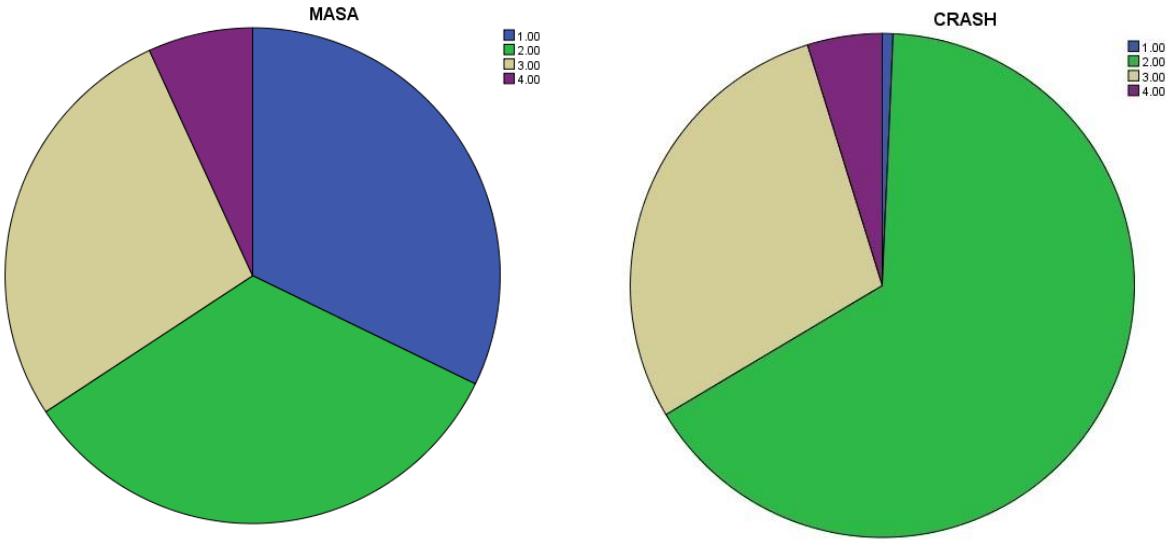

Figure 1: Pi distribution of MASA and CRASH family

: Patients had more than 4 MASA and CRASH symptoms.

In the present study, all the patients displayed a combination of various L1 syndrome features (Figure 2). Of all the L1 syndrome clinical features, Mental retardation and Aphasia have been found to be very prominent clinical symptoms in the present data.

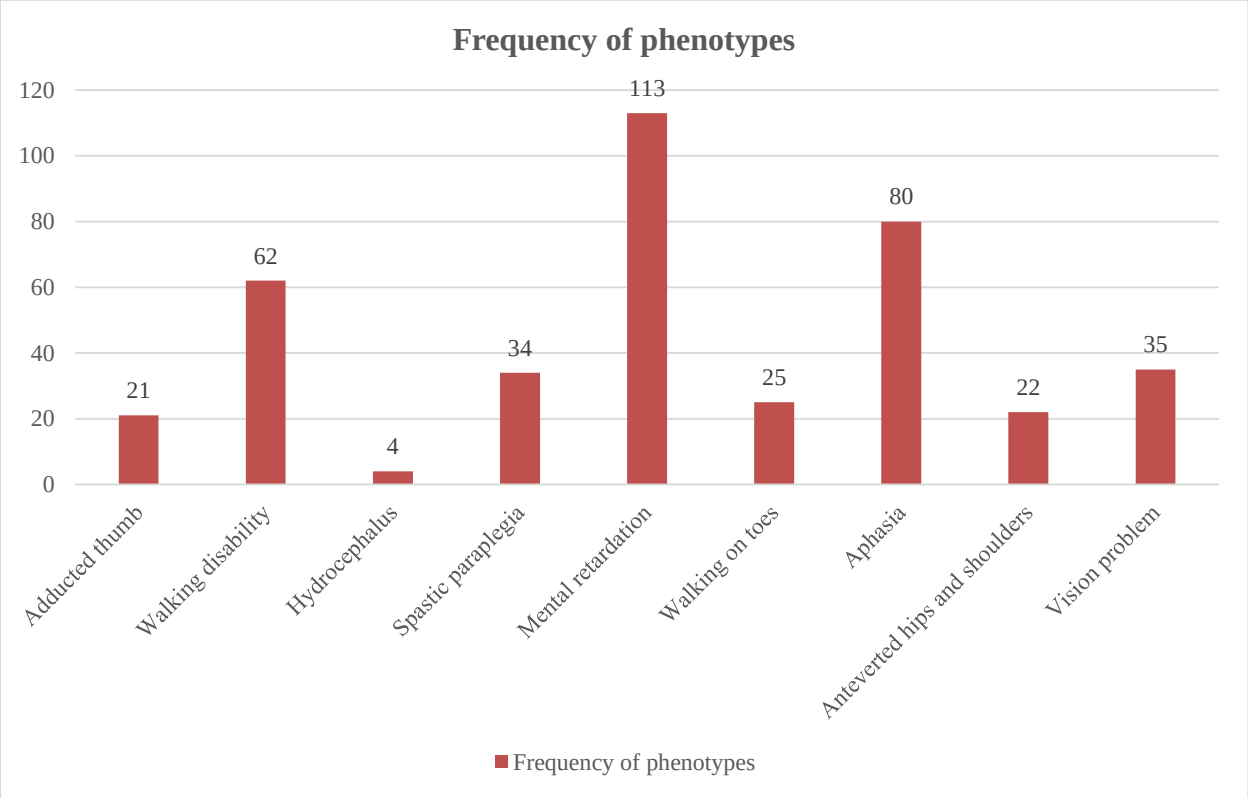

Figure 2: Graphical representation and frequency distribution of L1 syndrome features

Nearly 40 % of the patients were found to be associated with more than four L1 syndrome features. And nearly 82 % of the patients were associated with more than two L1 syndrome features (Figure 3).

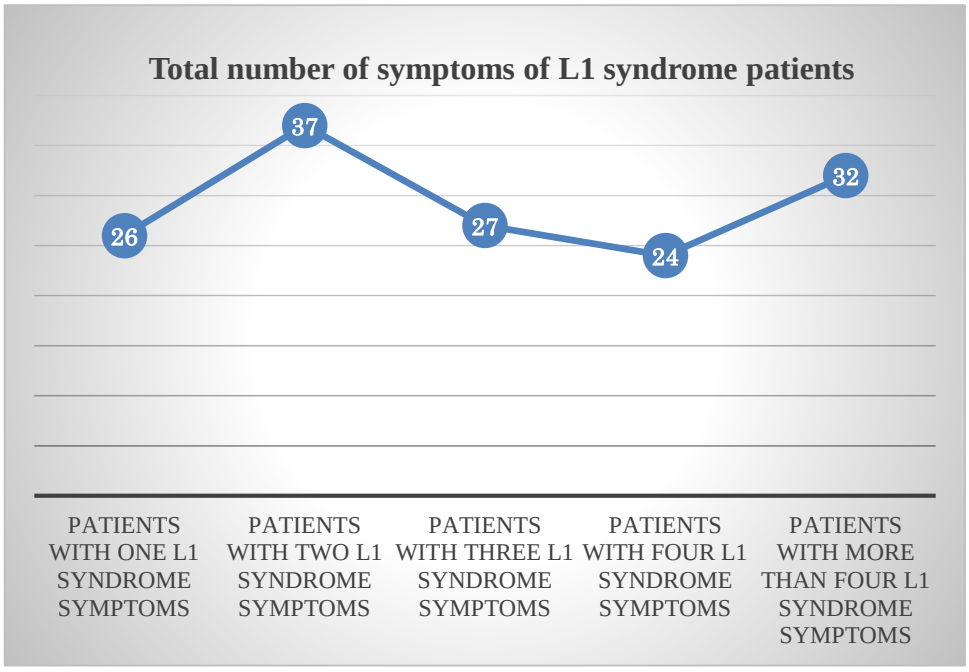

Figure 3: Frequency of patients with L1 syndrome features

Consanguinity and Family history

Among 146 patients, eight patients had been reported to have spontaneous abortions and early childhood deaths in their families. In the present study, 55 patients were found to have consanguineous parents or marriages (Table 2), and 48 patients have a family history for L1 syndrome (Table 3).

Table 2: Frequency of consanguinity

Consanguineous marriage	Frequency	Percent	Valid Percent
No	91	62.3	62.3
Yes	55	37.7	37.7
Total	146	100.0	100.0

Table 3: Frequency of family history

Family history	Frequency	Percent	Valid Percent
No	98	67.1	67.1
Yes	48	32.9	32.9
Total	146	100.0	100.0

The statistical test shown an F – distribution curve (Figure 4) of family history and consanguinity asymptotically intersect each other.

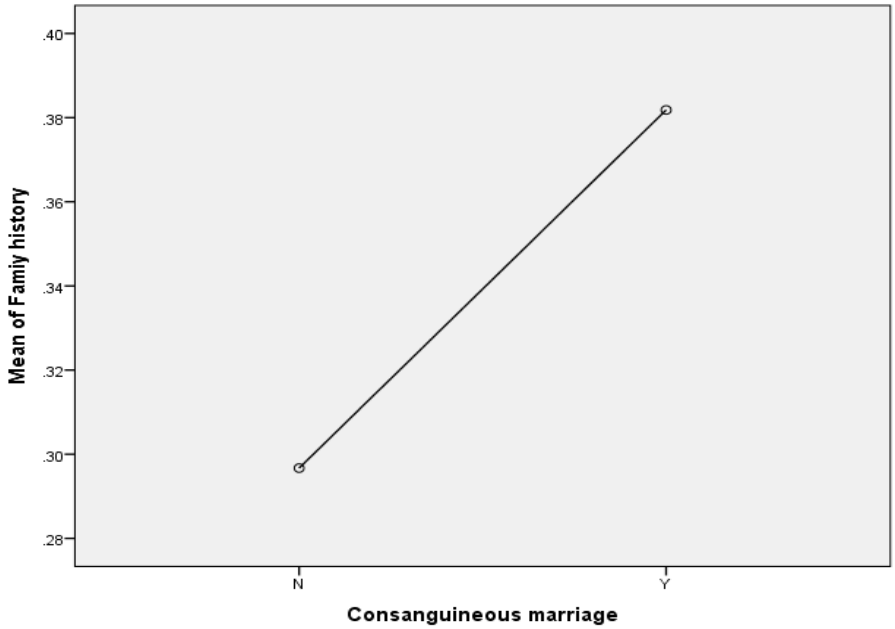

Figure 4: F – distribution curve of family history with consanguineous marriage

Among 146 individuals the maximum number of patients fall under the age group of 12 – 16 years and the frequency of affected members gradually increased from neonatal to adolescence. After that, the frequency decreases, it indicates that the survivorship in L1 syndrome condition was up to the specific age group (Table 4).

Table 4: Age wise distribution of L1 syndrome patients

Age at referral	Frequency	Percent	Valid Percent	Cumulative Percent
0.0-3	5	3.4	3.4	3.4
4-7	14	9.6	9.6	13.0
8-11	30	20.5	20.5	33.6
12-15	**43**	**29.5**	**29.5**	**63.0**
16-19	**32**	**21.9**	**21.9**	**84.9**
20-23	7	4.8	4.8	89.7
24-27	9	6.2	6.2	95.9
28-31	3	2.1	2.1	97.9
39-42	1	0.7	0.7	98.6
43-46	1	0.7	0.7	99.3
60-63	1	0.7	0.7	100.0
Total	146	100.0	100.0	

The approximate significance of L1 syndrome patients comes under adolescence age group at p=0.033 (X^2=14.45, df=1) and the significance was calculated purely based on the phenotypical characters.

DISCUSSION

With the heterogeneous condition of L1 syndrome, the broad clinical spectrum of malformations encountered. It is interesting to look for a phenotype correlation among L1 syndrome individuals. We collected the clinical data from 146 affected individuals. Based on the number and types of symptoms we segregated the patient's data into CRASH family and MASA family, these two are early subdivisions [15]. Among 146 patients 5 patients were stillbirths, it is impossible to estimate IQ of stillbirths. So, we mentioned them as developmental delay [18]. In L1 syndrome patients the Mental retardation has displayed a combination with L1 syndrome features. So, the rate of the predominance of L1 syndrome in mentally retarded patients is high. Clinical studies have indicated that the large overlap between Mental retardation and four phenotypes along with the presence of several combinations of these phenotypes in a single family indicates the presence of L1 syndrome mutations [16, 20, 21 And 22]. (Figure 5). This proved that HSAS, MASA, Complicated SP1, and other symptoms are not a separate condition but rather represent overlapping clinical spectra due to mutations in a single gene, L1CAM [22].

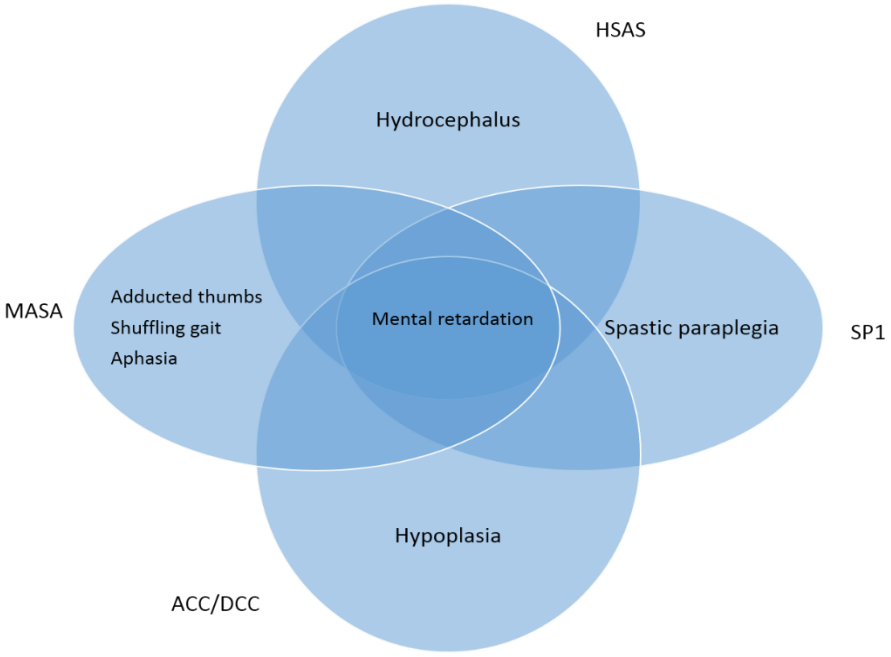

Figure 5: Schematic representation of the overlapping clinical spectra of HSAS, MASA syndrome, SPG – 1 [22].

One of the previous studies showed that, the rate of predominance of L1 syndrome in mentally retarded patients is high [23, 8]. In the present data among all phenotypes, the mental retardation, aphasia, and walking disability have been found to be very prominent. The study has suggested that consanguineous marriage is also one of the important factors in the development of the disease [13]. In the present study, 55 patients have consanguineous parents or marriages (Table 2 &3; Figure 4). A family reported in one of the previous study [16] had shown affected members in more than two generations. Another study described a family in which all of the 15 male individuals were affected by X-linked Hydrocephalus. However, the relation of consanguinity and L1 syndrome needs to be investigated. In the present study, the maximum number of patients fall under the age group of 12-16 years. This is in congruence with earlier study and had maximum affected members under the adolescence condition [19]. The present study revealed that the prevalence of L1 syndrome is promising and needs to be exploited for screening mutations in patients in Karnataka. By screening mutations in L1 CAM gene, it is possible to the high rate of mutation and will also help further understanding the pathogenesis of the L1 syndrome.

4. CONCLUSION

Our present study is preliminary on L1 syndrome in the Indian population in particular, it reveals that, the L1 syndrome is prevalent in Karnataka, India. And, In India, no investigations have been made earlier particularly on the prevalence of L1 syndrome [26, 27 and 25], and our study is the first report on the prevalence of L1 syndrome. In addition, the occurrence of several clinical features of L1CAM syndrome will be helpful for planning molecular testing both in familial and apparently sporadic cases [24].

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CONFLICT OF INTEREST

No financial interest or any conflict of interest does exist.

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