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A Report On 38 Cases Of Brachmann-De Lange Syndrome (BDLS)

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Abstract

During a survey of over six thousand MR in a decade, we encountered 38 cases, who fitted into the diagnosis of BDLS. The children were brought primarily with the complaint of delayed milestones of development and sluggish physical activity. On examination all showed short stature, microbrachycephaly, synophrys, characteristic nasal changes (triangular tip, lateral prominence and some anteverted nostrils), posterior rotating ears, hirsutism and limitation of extension of elbow. The dermatoglyphic pattern was also suggestive of BDLS. Cytogenetic investigations of 12 patients revealed a normal chromosomal complement. The clinical findings would be reported with points to be kept in mind for differential diagnosis.

Key words -

Brachamann-de Lange Syndrome,
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The Brachmann -de lange Syndrome (BDLS) is a syndrome, where there is retardation of both growth and mental development. Besides this, there may also be microbrachycephaly and hirsutism. The diagnosis is made exclusively on the clincial findings and there are no chromosomal or biochemical markers for this syndrome. Cornelia de lange [1] described the syndrome of having mental retardation associated with typical facies, low pitched cry, short stature, abnormally small limbs and flexion contractures of the elbow. In an editorial Opitz [2] has reported that Dr. W

Brachmann had described the syndrome 17 years earlier than de lange i.e., in 1916 and hence the redesignation Brachamann-de lange syndrome (BDLS). Brachmann had preserved (in alcohol) the child who had died at an age of 19 days. The body was of small size (43 cms) with microcephaly, brachycephaly, severe hirsutism, fleeting forehead, micrognathia, well formed ears, beaked nose, small arms, acutely flexed at elbow joint with webbing. Optiz [2] reported that BDLS is a relatively common disorder with an estimated prevalence of 1/10,000 births. Berg et al [3] listed different clinical signs which they consider as most helpful for purposes of diagnosis which include the following.

(i) hirsutism
(ii) long and or protruding philtrum
(iii) limited extension of elbows
(iv) low birth weight
(v) retarded mental and physical development
(vi) microcephaly
(vii) anteverted nostrils
(viii) thin lips with downturned corners
(ix) simian crease
(x) low set thumbs
(xi) 5th finger clinodactyly
(xii) severely malformed upper limbs
(xiii) webbed 2nd and 3rd toes.

In the clinical material of Berg et al [3], the first four features were present in all cases, but the remaining features were present in 12-51% with relatively higher frequency.

Material and Methods

This study is based on 6000 mentally retarded patients attending the mental retardation clinic, NIMHANS, Bangalore during the last one decade.

In all the cases, the clinical and genetic history were obtained. The patients having multiple congenital anomalies (MCA) and mental retardation were examined in detail. In all cases of MCA/MR detailed biochemical, dermatoglyphic and cytogenetic studies were carried out.

Results and Discussion

The present study detected 38 cases of children who could be clinically fitted into the diagnosis of Brachmann-de lange syndrome (BDLS). These included 22 males and 16 females. Table 1 shows the age range of cases of BDLS.

Table 1 - Age range of cases of BDLS (N=38)

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A majority of the BDLS patients were below the age of 14 years. Fifty percent of BDLS were 2 years or below. Since BDLS infants have several congenital anomalies and also often present with feeding problems and a low pitched weak growling cry, such children are felt to be abnormal and referred early

to MR clinic.

About 50 percent of the BDLS cases were from Bangalore city, two were from Madhya Pradesh and the remaining were from other parts of Karnataka state.

Fourteen BDLS cases with parental consanguinity (about 37%) were from consanguinious families, which is almost equal to consanguinity in general population. Thirty eight BDLS are from 37 families. In one family both the brothers were affected and father had minor physical features of BDLS with normal intelligence and there was no consanguinity.

Birth order distribution revealed that 10 (25%) were first born; 20 (56%) were last born and 8 (21%) were in the intermediate position. Since a majority of the BDLS cases were last born, parents voluntarily decided not to have any children after seeing the BDLS child (they could notice the abnormality surprisingly quite early).

Birth history revealed that 25 (66%) BDLS patients either had low birth weight or were prematurely born. In six cases the history of attacks of cyanosis and apnoea was present.The milestones of development were significantly delayed in all the BDLS cases. Another important feature noticed by the mothers of BDLS patients was that their children, specially in infancy and early childhood, showed slow or sluggish physical activity. Table 2 indicates the degree of mental retardation.

Table 2 - Degree of mental retardation (N=38)

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Fifty percent of BDLS patients in this series were two years or below, hence detailed psychometry could not be done. One child was profoundly retarded who had apnoea and cyanosis at birth and was getting convulsions and in addition, the child had ventricular septal defect, Tables 3-7 show the congential anomalies and their frequency observed in the present study.

Table 3 - The congenital anomalies and their frequency in the present study (N=38)

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Table 4 - Occular anomalies (N=38)

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Table 5 - Nasal and ear anomalies (N=38)

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Table 6 - Mouth and teeth anomalies (N=38)

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Table 7 - Anomalies of limbs, hands and feet (N =38)

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Figures 3-6 show the facial characteristics of BDLS patients.

Dermatoglyphic features characteristic of BDLS patients as seen in left hand.

- ***Dermatoglyphic features characteristic of BDLS patients as seen in right hand.***
- ***A male child aged 3/12 months showing most of the features characteristics of BDLS which includes : curved eyebrows meet at midline, excessive hair on the forehead, long philtrum, thin lips with down turned corners, tip of nose pointed, flaring of the nostrils and thumb proximally placed***
- ***A male child aged 5 years showing the following clinical features: short stature, curved eyebrows meet at midline, short forehead and excessive hair present, long philtrum, nose short and tip pointed, lips thin and angle of mouth curved, non-extendable elbows, thumb proximally placed and undescended testes***
- ***A male child 13 years old showing some of the following clinical features: eyebrows meet at midline, excessive hair on forehead, long philtrum with prominence, tip of the nose is also prominent, well formed ears and lips thin***
- ***A female child aged 8 years showing some of the following features : eyebrows meet at midline, excessive hair on forehead, long philtrum and well formed ears***

Hirsutism was commonly seen on the back forehead, and in many it was present all over the body. One male BDLS aged 15 years had not developed any secondary sexual characteristics and his testes were atrophied.

All the BDLS cases had synophrys, abnormality in eyebrows and long eyelashes. All cases of BDLS need detailed testing of vision, since, some of them have myopia, which needs to be corrected early.

Nasal abnormalities are quite common and are characteristic of BDLS. Behaviour problems are quite common and are almost the same as noticed in all severely mentally retarded. Seizures were found in only three children (7.9%) with BDLS. (Table 13).

Table 8 - Dermatoglyphic pattern in de lange Syndrome cases (N=32)

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Table 9 - Radial loops in individual digits

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Table 10 - Mean total finger ridge counts

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Table 11 - ATD angle

Table 11 - ATD angle

Table 12 - Some other important features

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Table 13 - Behaviour problems (N=38)

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Dermatoglyphic patterns could not be studied in all the 38 children, since 6 were very young and non-cooperative.

Radial loops are increased particularly in the third digit, whorls are markedly decreased. Position of the distal axial triradii also increased, loops in I^3 area and oblique or transverse loop in I^4 area also had

increased frequency. Compared to normal controls, total finger ridge count is also decreased. The axial triradius is displaced resulting in a wide ATD angle. (Tables 8 to 12; Figs. 1 &2).

Cytogenetic studies were done on 12 BDLS patients and all their karyotypes revealed normal chromosome complement, except in a few cases, where there is a large secondary constiction on chromosome 9 and in one case, in one spread there was translocation of (7:14) resulting in 14q deletion and in another case the Y chromosome was large, In general, there was no structural abnormalities or aneuploidy and no visible chromosome changes were seen.

Followup and Management

Early diagnosis is obligatory. The major management problems noticed in them were feeding problems and projectile vomiting, behaviour problems included temper tantrums, hearing and dental difficulties, recurrent respiratory infections. Other important problems are seizures (14.3%) and congenital heart diseases (28%).

All cases are being followed up and parents are training the children in self-help skills and some have joined special schools.

Conclusions

1. The BDLS is a relatively common disorder (1/10,000).
2. It is an enormously variable MCA/MR Syndrome, ranging from perinatal lethality with multiple congenital anomalies.
3. In most cases it appears to be a sporadic disorder.
4. Though consanguinity was seen in 37 % of cases, it appears to be not higher than in general population. Except for one family, in all other cases no other sibling was affected. In one family the father had a few BDLS features but was intelligent and this may have been due to dominant gene transmission.
5. In 5 cases minor chromosomal variation such as 9qh+ was seen in general population. Chromosomal anomalies seen in BDLS seem to be an effect rather than a cause, some may be a matter of coincidence.

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