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(CASE REPORT)

Interstitial deletion of the long arm of chromosome 3, del (3) (q25-q27), in association with Dandy Walker malformation: A case report

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Abstract

Interstitial deletions of the long arm of chromosome 3 are rare, and detailed genotype-phenotype correlations are not well established. The Dandy-Walker malformation (DWM) is one of the most common congenital cerebellar defects and can be associated with multiple congenital anomalies and chromosomal syndromes.

We report an interstitial deletion of 3q: 46, XY, del (3) (q25; q27) in a Three-month-old boy with dysmorphic features, developmental delay, and a Dandy Walker malformation observed in MRI.

Keywords: Interstitial Deletion; 3q25.27 region; Karyotype; Dysmorphic Features; Dandy Walker Malformation.

1. Introduction

Deletions can occur at the proximal or distal portions of a chromosome, involving different breakpoints.

Interstitial deletions of the long arm of chromosome 3 are very rare, and detailed genotype-phenotype correlations are not well established.

Dandy-Walker malformation is a brain malformation of unknown etiology, but several reports suggest a causal relationship with various chromosomal abnormalities and malformation syndromes. Various chromosomal abnormalities are associated with DWM; most frequently involving chromosome 3, 9, 13 and 18.

Here, we describe a case with an interstitial deletion involving 3q25.27 region, associated with Dandy-Walker malformation.

2. Case presentation

We report a three-Month-Old male infant from a non-consanguineous marriage. The family history was not contributory. The pregnancy was uncomplicated, with no particular issues, The infant was evaluated for dysmorphic features including microcephaly, microphtalmia, blepharophimosis, ptosis, epicanthus inversus, poorly folded ears, cleft palate, hypertelorism, retrognathia, an umbilical hernia, psychomotor delay, and growth retardation of 3SD.

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An abdominal-pelvic ultrasound and Standard X –rays of the pelvis and hips were normal.

A hip ultrasound revealed femoral head-pubic distances greater than 4mm, suggesting mild dysplasia.

A brain MRI revealed a Dandy-Walker malformation.

The constitutional karyotype showed the presence of an interstitial deletion of the long arm of a chromosome 3:46, XY, del(3) (q25q 27).

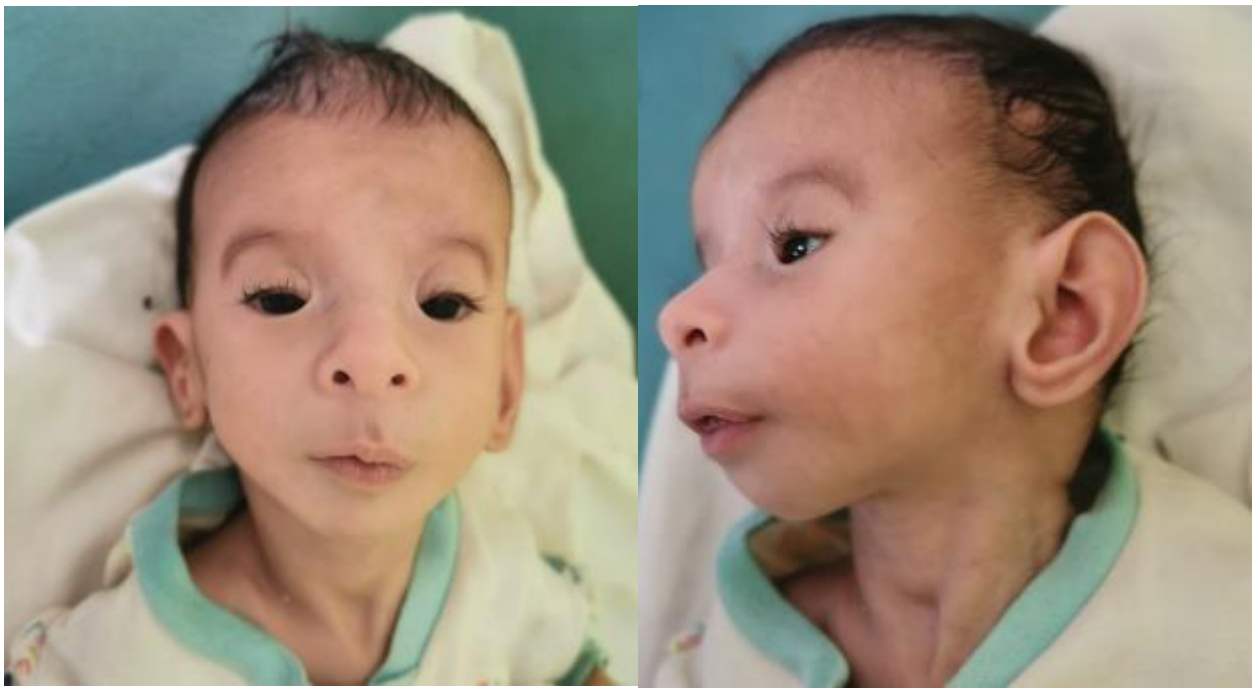

Figure 1 Photograph shows the propositus with dysmorphic features due to an interstitial deletion of the long arm of chromosome 3

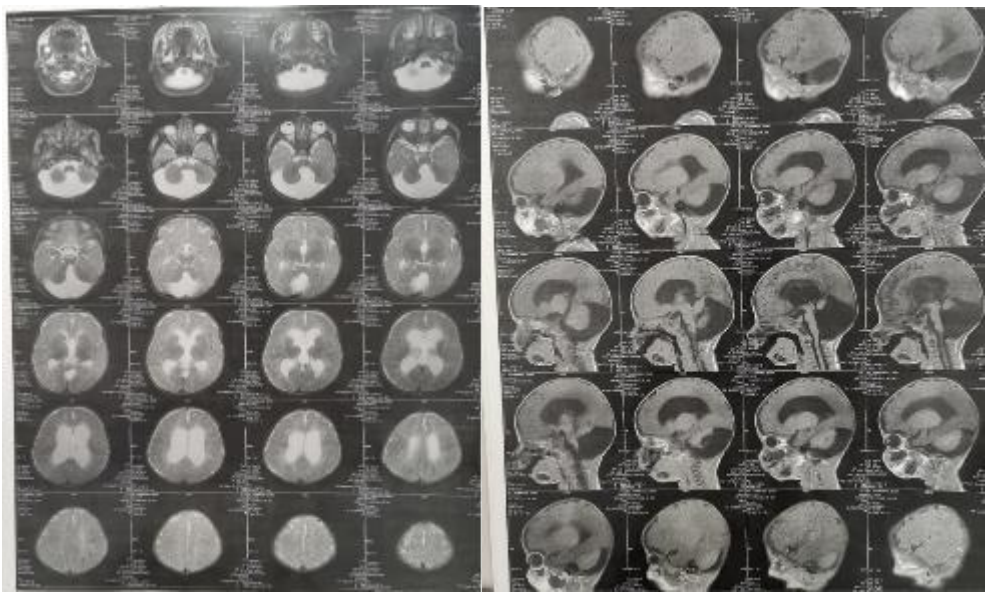

Figure 2 Brain MRIs. Brain imaging of our patient with Dandy-Walker malformation

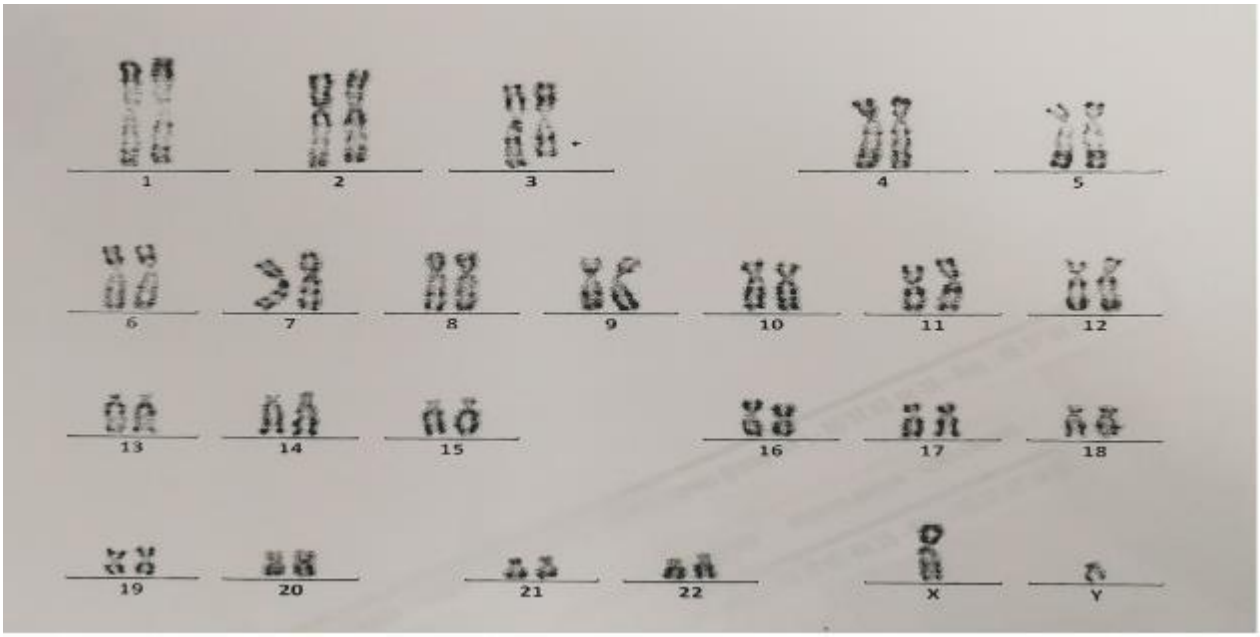

Figure 3 Karyotype of our patient shows an interstitial deletion of the long arm of chromosome 3, del (3) (q25-q27)

3. Discussion

Chromosomal analysis has always been the gold standard for diagnosing patients with dysmorphic features and learning disabilities.

Chromosomal imbalances, such as deletions, can involve either terminal or interstitial segments of the chromosomes. These deletions may affect either the p arm or the q arm of the chromosome.

Chromosome 3 is approximately 200 Mb in size. Within this chromosome, there are thousands of genes, many of which are necessary for normal intellectual development and the formation of body organs.

Interstitial deletions involving the long arm of chromosome 3 are rare, and detailed genotype-phenotype correlations have not been well established to date. Proximal 3q deletion syndrome was delineated by Simovich et al. They concluded that these patients have a distinct, recognizable facial dysmorphism and are at risk for developmental delay and other structural abnormalities of the brain, genitourinary, and musculoskeletal systems. Furthermore, distal deletions involving the 3q25 region exhibit variable chromosomal breakpoints and deletion sizes, ranging from 3q23 to 3q26.1 [1-2]. All patients presented with facial dysmorphism and developmental delay, but other phenotypic features, such as cardiac defect, microcephaly, epicanthus and short stature were not always present.

The first case of an interstitial deletion of the long arm of chromosome 3 (q23q25) was described in 1983 by J. T. Martsolf [3] in a 20-year-old female with mental retardation, short stature, facial dysmorphism, musculoskeletal abnormalities, and deafness. Her karyotype was 46, XX, del(3)(q23q25). Considering the small number of reported cases, the wide variability of the previously described deletions, and the lack of molecular data about the size of the deletions, delineating a precise deletion syndrome involving the 3q25 band is still challenging.

With the exception of blepharophimosis and ptosis, most of the dysmorphic features are non-specific, such as developmental and growth delay, epicanthic folds, displaced and dysmorphic ears, and congenital heart disease [4-5]. A rarer physical sign that has previously been described is digital anomalies in a patient with an interstitial deletion of 3q23q25 [6]. Associated neuropsychiatric disorders have been mentioned in one case report, involving autistic and obsessive behavioral traits associated with a 3q25 deletion [7, 8].

Reports of interstitial and terminal deletions distal to 3q25 have also not yet resulted in a distinct 3q deletion phenotype, possibly owing to the paucity of documented cases [4-5].

The Dandy-Walker malformation (DWM) is one of the most common congenital cerebellar defects. It is characterized by hypoplasia and upward rotation of the cerebellar vermis accompanied by a retrocerebellar cyst in communication with the fourth ventricle (Patel and Barkovich 2002) [9]. DWM can be associated with multiple congenital anomalies and chromosomal syndromes. Although its etiology is unknown, several reports suggest a causal relationship with various chromosomal abnormalities and malformation syndromes. There are various types of chromosomal abnormalities associated with DWM; most of them are reported on chromosomes 3, 9, 13 and 18. The occurrence of overlapping 3q deletions, including the ZIC1 and ZIC4 genes in few patients, along with data from mouse models, has implicated both genes in the pathogenesis of DWM.

In 2004, overlapping deletions including the 3q24q25.1 chromosome region were reported in eight DWM patients displaying marked clinical and neuro-radiological variability. Haploinsufficiency of the ZIC1 and ZIC4 genes, mapping within the deleted region, has been implicated as causative of DWM, based on mouse models. Seven patients shared a 7 Mb critical region including both genes. In another patient, in which the deletion did not contain ZIC1 and ZIC4, the expression level of both genes was found to be halved, suggesting a position effect [10]. Following this report, at least six additional cases with features of the DWM spectrum have been published, all carrying a 3q chromosomal deletion encompassing the ZIC1 and ZIC4 genes [3-4].

In 2004, Girnberg et al. [11] conducted a genetic analysis of six cases of DWM with interstitial deletions observed in 3q, and defined the first critical region associated with DWM in 3q24, encompassing two adjacent zinc finger cerebellum genes, ZIC1 and ZIC4 (Girnberg et al. 2004 [11]; Grinberg & Millen 2005 [12]; Titomanlino et al. 2005 [13]. Furthermore, the authors pathologically proved that mice with heterozygous deletions of these two linked genes had a phenotype that closely resembled DWM, providing a mouse model of this malformation.

There have also been four case reports of DWM complicated by chromosome 3 abnormalities, including partial trisomy 3p and partial monosomy 11q (Chen et al. 2002b [14]). Partial trisomy 3q (de Azevedo et al. 2005[15]), dup(3q) syndrome (Ounap et al. 2005[16]), and an interstitial deletion of chromosome 3q [3q25.1–3q25.33] (Sudha et al. 2001[17]).

Complications of chromosomal abnormalities in various cases of brain malformation have been reported, and new causative genes have been identified one after another in recent years. It is important to accumulate more cases of DWM associated with chromosomal abnormalities, as DWM often involves complications from various chromosomal abnormalities and malformation syndromes. There is a high possibility that further candidate genes may be identified in other regions in the near future.

The four highly significant so called malformation-associated bands (MABs) 3q26.1, 3q26.2 and 3q26.3 ($P< 0.001$) and 3q25 ($P< 0.01$, $P> 0.001$) (clinical descriptions (Sudha et al. [17] 2001; Willner et al. 1990 [18]) are likely to represent a single locus; indeed, an association of 3q deletions (3q24.3-q25.33) and DWM has been previously shown. ZIC1 and ZIC4 have been suggested as possible causative genes (Grinberg et al. 2004 [11]).

Dandy-walker malformation may be caused by deletions of two linked genes, ZIC1 and ZIC4, both of which reside in the distal part of 3q24 (very close to 3q25.1). Approximately 15 patients with deletions within the 3q24q25.1region have exhibited this defect. In addition to the common manifestations of DWM, affected children are usually developmentally delayed, and some have microcephaly. The spectrum of associated defects depends on the length and content of the other parts of 3q lost during the deletion.

It should be noted that DWM is not an obligatory manifestation of a 3q24q25.1 deletion. Several patients with this deletion, including those whose breakpoints were confirmed by molecular method, do not have DWM but do exhibit seizures, microcephaly, and defect in the occipital area of the scalp. All reported deletions in this group have been sporadic so far [19].

4. Conclusion

In summary, due to the heterogeneity in the size and position of the deletions, a clear genotype-phenotype correlation for interstitial deletions of chromosome 3 remains unclear.

Complications of chromosomal abnormalities in various cases of brain malformation have been reported, and new causative genes have been identified one after another in recent years. As summarized in the present article, many case reports of DWS with complications of chromosomal abnormalities have been published in the past. However, only ZIC1 and ZIC4 genes of chromosome 3q24 have been identified as candidate genes in recent years. It is important to

accumulate cases regarding DWS and chromosomal abnormalities because DWS involves cases with complications of various chromosomal abnormalities and malformation syndromes and there is a high possibility that further candidate genes may be identified in other regions in the near future.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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