*Case Report*

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# Nijmegen Breakage Syndrome: A Retrospective Analysis of Two Sisters Studied in India Before the First Published Report

**Pavri-Madon Prochi F.**

## Abstract

Nijmegen breakage syndrome (NBS) is a rare autosomal recessive chromosomal breakage disorder characterized by microcephaly, growth delay, primary ovarian insufficiency and predisposition to recurrent infections. Chromosomal instability is demonstrated by breaks and rearrangements. This condition was first described in 1979 in a mentally retarded Dutch boy. In 1981, it was found that his elder brother had the same clinical symptoms with severe immunodeficiency and the parents had close consanguinity. This led to the description of a new chromosome instability disorder which was named after the place in the Netherlands, where it was discovered. The case described here of two affected sistersis a retrospective report of an Indian family studied in 1976 in Mumbai, five years before this syndrome was named.

**Keywords:** Nijmegen Breakage Syndrome; Chromosome Instability; Recurrent Infections.

## Introduction

Chromosome instability disorders are clinically diverse autosomal recessive human diseases which show an abnormal behavior of their chromosomes when exposed to mutagenic chemicals or irradiation [1]. Common examples are Fanconi anemia and ataxia telangiectasia. Nijmejen breakage syndrome (NBS) is a rare chromosome breakage disorder characterized by microcephaly, growth delay, primary ovarian insufficiency and predisposition to recurrent infections [2]. It was first described in 1979 in a mentally retarded Dutch boy with microcephaly, growth retardation, IgA deficiency and multiple rearrangements between chromosomes 7 and 14 [3]. In 1981, it was found that his elder brother had the same clinical symptoms with severe immunodeficiency and the parents had close consanguinity. This led to the description of a new chromosome instability disorder which was named after the place Nijmegen in the Netherlands, where it was discovered [4]. There are only 2 reports of this disorder from India, describing three unrelated cases, the first being in 2006 [5,6]. Mutations are known to occur in the NBN gene [7]. The case described here is a retrospective report of two sisters studied in 1976 in Mumbai. They were born of a consanguineous marriage and had clinical features similar to those now known to occur in Nijmegen breakage syndrome. They also demonstrated chromosome instability at the time of initial karyotyping. Translocations especially between chromosomes 7 and 14were not detected as Giemsabanding was not a routine procedure in India at that time.

## Case Report

Two sisters (KP and LP) aged 22 and 20 years from Maharashtra were brought to the Genetic Clinic and Pharmacogenetic Unit of J. J. Hospital in 1976, with a complaint of primary amenorrhoea, stunted growth with heights of 126 cm. and 130 cm. respectively, and mental retardation with the mental age on performance being 6-7 years. They had microcephaly, the head circumference being 44.5 cm. and 44 cm. Their bone age was 15-17 years. They had deep seated eyes and mandibular hypoplasia, with a similarity

**Author's Affiliation:** Genetic Clinic and Pharmacogenetic Unit, Department of Pharmacology, Sir J. J. Group of Hospitals and Grant Medical College, Mumbai 400008, India.

**Corresponding Author: Prochi F. Madon,** Genetics and PGD Laboratory, Department of Assisted Reproduction and Genetics, Jaslok Hospital and Research Centre, 15 Dr. G. DeshmukhMarg, Mumbai 400026, India.
E-mail: prochimadon@gmail.com

to bird-headed dwarfism (Figure 1). Their secondary sexual characteristics were underdeveloped. KP had a hypoplastic uterus, while the uterus could not be palpated in LP. Opthalmologic examination showed that in both sisters, the macula appeared pigmented and granular. Their birth weight was low and delivery was in the 8th month. Two elder sisters and two brothers were normal. Another 4 sibs died in infancy. KP had a history of recurrent respiratory tract infections, suggesting immunodeficiency. The parents had a consanguineous marriage. There was no history of other relatives with a similar disorder.

Karyotyping revealed a pattern of 46, XX in both sisters. However, multiple spontaneous breaks, fragments and double minutes were observed in about 40% metaphases (Figure 2a). Near triploidy (Figure 2b) was occasionally seen while tetraploidy (Figure 2c) was present in about 20% metaphases. Chromosome exchange figures(Figure 2d) were occasionally observed Lymphocyte cultures were carried out in TC-199 (folic acid deficient medium) which was routinely used for karyotyping at that time. The sisters had been exposed to diagnostic X-rays for bone age 3-4 days prior to blood collection. The parents, normal sibs and other patients karyotyped simultaneously under the same conditions did not show chromosome breaks or polyploidy. Repeat karyotyping after 3 weeks did not show breaks, though polyploidy was still seen in 20% metaphases in both sisters. Subsequently, chromosome analysis was carried out with various batches of serum, PHA and media, but tetraploidy or spontaneous breaks were not observed. A few months later, karyotyping was done after another X-ray but no chromosome damage was seen, hence the cause of the initial chromosome breakage was not clear.

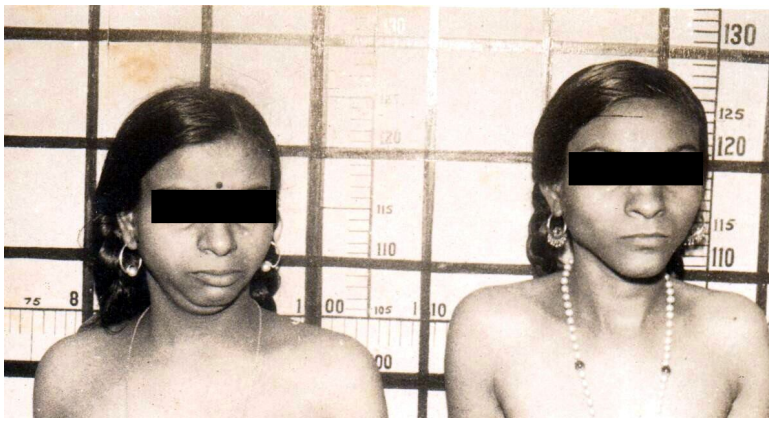


**Fig. 1:** The sisters with short stature and microcephaly

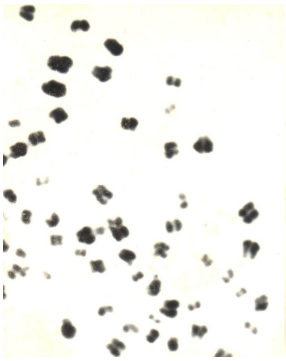

**Fig. 2a:** Multiple spontaneous chromosome breaks, fragments and double minutes

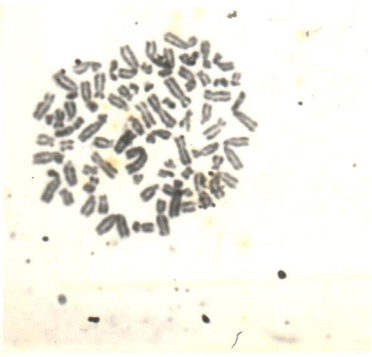

**Fig. 2b:** Triploidy

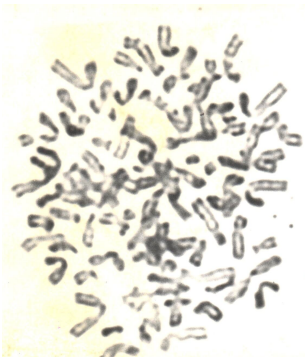

**Fig. 2c:** Tetraploidy

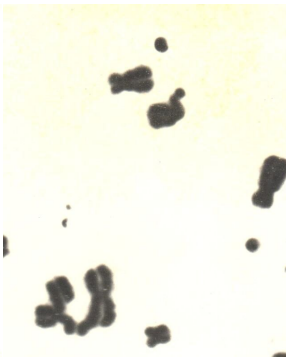

**Fig. 2d:** Chromosome breaks and exchanges

## Discussion

Retrospective analysis now with the current information on the clinical and cytogenetic features of chromosome breakage syndromes suggests that the sisters had a chromosome instability disorder, likely to be Nijmegen breakage syndrome. It went unreported in 1976as this syndrome had not been reported at that time. With relocation of staff and laboratory where the study was carried out, and limited facilities for literature search 30-40 years ago, the first reports of Nijmegen breakage syndrome and the similarity to our case remained unnoticed.The

case file was found recently henceit is being reported retrospectively. It is interesting to note that this family was studied in India before the first similar case was reported from Denmark and named after the cityNijmegen where it was discovered [4]. All the features of this syndrome, such as microcephaly, a bird-like face, growth delay, primary ovarian insufficiency, predisposition to recurrent respiratory infections, deterioration of cognitive functions and chromosomal instability were present in the two sisters described above. Attempts to contact the family recently to offer genetic counseling due to this disorder's currently known predisposition to cancer were not successful.

This highlights the importance of early reporting of interesting cases. If we had not hesitated to report our observation in 1976, this syndrome would have had a different name!

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**References**

1. Howell RT. Chromosome instability syndromes. In: Rooney DE (editor). Human Cytogenetics: malignancy and acquired abnormalities. Oxford. 2000; 227-254.
2. Chrzanowska KH, Gregorek H, Dembowska-Bagiñska B, Kalina MA, Digweed M. Nijmegen breakage syndrome (NBS). Orphanet Journal of Rare Diseases. 2012; 7: 13.
3. Hustinx TW, Scheres JM, Weemaes CM, terHaar BG, Janssen AH. Karyotype instability with multiple 7/14 and 7/7 rearrangements. Hum Genet. 1979; 49: 199-208.
4. Weemaes CM, Hustinx TW, Scheres JM, van Munster PJ, Bakkeren JA, Taalman RD. A new chromosomal instability disorder: the Nijmegen breakage syndrome. Acta Pediatr Scand. 1981; 70: 557-64.
5. Rao VB, Kerketta L, Korgaonkar S, Ghosh K. Differentiation of Nijmegen breakage syndrome fromFanconi anemia.Genetics and Molecular Research. 2007; 6: 622-6.
6. Patil M, Gothi D, Joshi JM. Nijmegen Syndrome in an Indian Male. Indian J Chest Dis Allied Sci. 2008; 50: 229-31.
7. Maurer MH, Hoffmann K, Sperling K, Varon R. High prevalence of the NBN gene mutation c.657-661del5 in Southeast Germany. J Appl Genet. 2010; 51: 211-4.