REVIEW ARTICLE

Major Chromosomal Abnormalities and Necrotizing Enterocolitis: Is there a Link?

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Abstract

Necrotizing enterocolitis (NEC) is a rare but potentially lethal disease of neonates, and several case reports have associated it with chromosomal disorders. As we know, chromosomal disorders affect approximately 0.6% of live births. Many infants with these abnormalities have no or only mild symptoms, but others can have significant morbidity and mortality. In this review, we summarize the available information about the occurrence of NEC in infants with chromosomal abnormalities. An intriguing aspect of these reports is that many infants with chromosomal abnormalities who developed NEC were near term in gestational age, and would not have otherwise been considered to be at particular risk of this disease. Existing reports have associated NEC with abnormalities of chromosomes 21 (Down syndrome), and 1, 6, 15, and 22. The main limitation of these observations is that the cohorts were not numerically adequate in a statistical sense, and hence the possibility of coincidence cannot be excluded with confidence. The impact of comorbidities or other possible confounders is also not clear. We need studies that are designed specifically, with appropriately large cohorts, to determine the frequency of comorbidities such as NEC in infants with chromosomal abnormalities.

Keywords: Chromosome, Chromosomal deletion, Chromosomal duplication, Chromosomal translocation, Down syndrome, Genetics, Neonate, Necrotizing enterocolitis, Robertsonian translocation, Trisomy.

Newborn (2022): 10.5005/jp-journals-11002-0032

Introduction

The global incidence of chromosomal abnormalities is estimated to be 1 per 153 live births, posing a significant challenge to the affected individuals, their families, health care systems, and society. Necrotizing enterocolitis is a severe, life-threatening intestinal disorder that is primarily known as one of the dreaded complications of premature birth, and its incidence among prematurely born neonates (GA 24–31 weeks) is overall approximately 5%, with approximately double the incidence at 24–27 weeks gestation (6.6%) as compared to 28–31 weeks gestation (2.6%).[1] This review focuses on a so-far mostly overlooked area of association between major chromosomal disorders and NEC.

Classification and Epidemiology of Chromosomal Disorders

The two main forms of chromosomal disorders are numerical and structural. Flowchart 1 summarizes the subtypes of these disorders, which are also briefly described below.

Numerical chromosomal disorders can be characterized as trisomy, monosomy, or triploidy (an extra set of chromosomes from one of the parents, present in each cell). These abnormalities can involve the (a) Sex chromosomes, such as Klinefelter syndrome and Turner syndrome; or the (b) Somatic chromosomes such as trisomy 13, trisomy 18, or trisomy 21.

Structural chromosomal disorders refer to an altered organization of genetic material within individual chromosomes. These include:

(a) Deletions: A part of a chromosome is left out during DNA replication.

(b) Duplications: A region of DNA containing a gene is duplicated.

(c) Translocations: Unusual rearrangement of chromosomes. Translocations can be balanced, with an even exchange of material with no loss or gain of genetic information, or unbalanced, where the unequal exchange of chromosome material results in extra or missing genes. Unbalanced translocations are of two types: (a) Reciprocal, where the chromosome abnormality is caused by exchange of parts between non-homologous chromosomes. The detached fragments of two different chromosomes are switched and (b) Robertsonian; arms of two non-homologous chromosomes break at the centromeres and are exchanged.

(d) Inversions: A segment of a chromosome is reversed end to end; can be

(i) *Paracentric:* Includes the centromere; both breaks occur in one arm of the chromosome or

(ii) *Pericentric:* Includes the centromere and has a break-point in each arm.

(e) Isochromosomes: Unbalanced abnormality in which the two copies of either the long (q) or the short (p) arm join each other. Isochromosomes form due to simultaneous duplication and deletion of genetic material and, therefore, have partial trisomy of the genes present in the isochromosome and partial monosomy of the genes in the lost arm.

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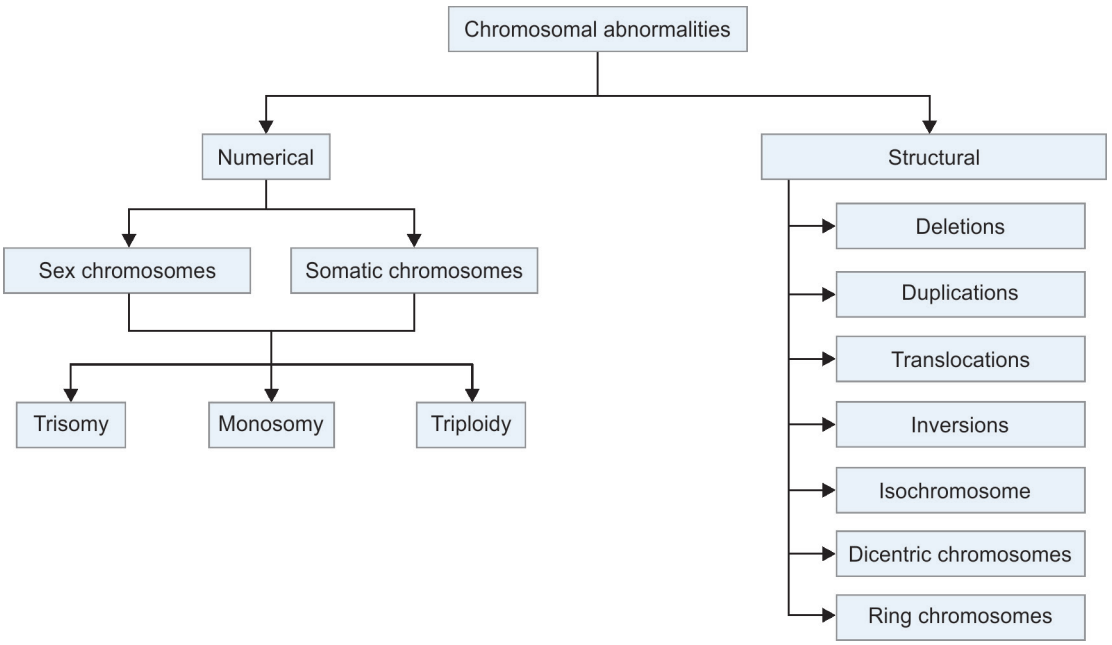
How to cite this article: Maheshwari A, Jilling T. Major Chromosomal Abnormalities and Necrotizing Enterocolitis: Is there a Link? Newborn 2022;1(2):233–237.

Source of support: Nil

Conflict of interest: None

Flowchart 1: The types of chromosomal abnormalities we considered in this review



(f) *Dicentric chromosomes*: Abnormal chromosomes with two centromeres; formed due to fusion of two chromosome segments, each with a centromere. The acentric fragments lacking a centromere are lost. Dicentric chromosomes may form due to

(i) Robertsonian translocation in acrocentric chromosome pairs (that have one very short arm), namely 13, 14, 15, 21, and 22. The participating chromosomes break at their centromeres and the long arms fuse to form a single, large chromosome with a single centromere and

(ii) Paracentric inversion.

(g) *Ring chromosomes*: Aberrant chromosomes with ends fused together to form a ring; both ends of the chromosome are usually missing, enabling the broken ends to fuse together.

Epidemiology of Chromosomal Disorders

The global epidemiology of chromosomal disorders is summarized in Table 1, adapted from a review by Verma and Puri.[2] The most frequent of all chromosomal disorders, which is also the most common numerical chromosomal abnormality, is trisomy 21 or Down syndrome, which occurs in 1 per 729 live births. The second most common chromosomal disorder overall, and the most common sex chromosome disorder, is the extra-numerary Y-chromosome, which affects 1 infant in 815 live births. The best known and most common extra-numerary Y-chromosome disorder is the Klinefelter syndrome, 47 XXY, which is the most frequent condition with an extra-numerary Y chromosome. Other forms include 47 XYY, 48 XXXY, and 48 XYYY (Table 1).

The most frequent structural chromosomal disorders are balanced chromosomal translocations (1 per 500 live births), which result in no gain or loss of overall genetic material, but show parts of genetic material joined with each other (Robertsonian translocation) or swapping of places within or between chromosomes. Balanced chromosomal translocations commonly have no overt phenotype but may sometimes result in infertility. If fertility remains intact, the offspring may be predisposed to chromosomal disorders such as unbalanced chromosomal translocations. Some of the balanced translocations, particularly when a chromosome breakage point interrupts a gene, may result in a clinically apparent phenotypic change. Unbalanced chromosomal structural abnormalities occur less frequently than balanced translocations (1 per 4500 live births), and they result in the gain or loss of genetic material. One subtype of these abnormalities are the unbalanced translocations, where an extra part of a chromosome is lost or added on another chromosome. Such abnormalities may include the so-called partial trisomies or monosomies, and these are almost always symptomatic.

Table 1: Chromosomal abnormalities in liveborn babies (n = 120, 290; 70,115 males and 50,175 females) (Adapted from Verma and Puri, 2015)

	Rate	
Abnormality	*Per 1000*	*1 in*
47 XYY		
47 XXY, or 48 XXXY, or 48 XYY	1.23	815
45 X	0.14	7,168
47 XXX	0.94	1,068
+D	0.06	24.058
+E	0.21	4,812
+G	1.37	729
Balanced Robertsonian translocations	0.91	1,098
Translocations, insertions	0.97	1,028
Unbalanced structural abnormalities	0.22	4,545
Marker chromosomes	0.41	2,455
Total	6.52	153

+D = Trisomy 13, +E = Trisomy 18, +G = Trisomy 21

Germline vs Somatic Origin of Chromosomal Abnormality

If a chromosomal defect originates prior to conception during oogenesis or spermatogenesis, it results in germline chromosomal defects that can be seen in all the cells of the neonate, and are likely to be inherited by his/her offsprings. In contrast, chromosomal defects that occur later in one or more of the downstream somatic

cells are likely to affect only the cells downstream from these progenitor(s). Such defects cause mosaicism, where the neonate will have chromosomal defects in some, not all, cells.

Chromosomal Abnormalities Recorded in Infants with Necrotizing Enterocolitis

The etiology of NEC is considered to be multifactorial, including both host and environmental influences. Key environmental factors include feeding modalities, antibiotic use, transfusions, use of steroids and non-steroidal anti-inflammatory drugs, and perinatal infections. The most important host factor determining the susceptibility to NEC is prematurity, as NEC is almost non-existent in full term neonates and its incidence can be >10% in extremely low birth weight [(ELBW); <1000 gm birth weight] neonates. Additional host factors contributing to predisposition to NEC include various comorbidities, the microbiomes of both the mother and the neonate, and genetics. Of the contributing genetic factors, the association of mutations or single-nucleotide polymorphisms (SNPs) in individual genes with the incidence of NEC have been most investigated; reviewed by Cuna et al.[3] Additionally, association between NEC with genome-wide SNPs and with organ-specific and gene-specific epigenetic changes have been analyzed, which have been summarized in other reviews in this issue.[4–6]

Numerical Chromosomal Disorders and NEC

Trisomy 21; Down syndrome: A large cohort study from the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network (NRN) analyzed morbidity and mortality in neonates with trisomy 13 (T13; $n = 36$), trisomy 18 (T18; $n = 125$), and trisomy 21 (T21; $n = 139$) and compared them to 49,600 neonates without birth defects.[7] Intriguingly, there were 20 (16%) cases of NEC in the T21 cohort, but there were none in the T13 and T18 cohorts among neonates that survived ≥12 h after birth. These differences could be potentially explained by the significantly higher percentage of neonates with gestational ages <26 weeks in the T21 group ($n = 22$, 16%) than in the T18 group ($n = 3$, 3%); T13 was not significantly different ($n = 2$, 6%). However, for instance, the incidence of BPD was not different between T21 ($n = 38$, 39%), T18 ($n = 8$, 62%), and T13 ($n = 3$; 60%) among infants who survived >36 weeks postmenstrual age, and the incidence of respiratory distress syndrome was lower in the T21 ($n = 88$, 67%) than in the T18 ($n = 71$, 82%) and was not significantly different from T13 ($n = 14$; 82%). Furthermore, in a study of 29 term (>37 weeks gestational age) neonates with NEC, there were two cases (6.9%) of T21,[8] and in another full-term NEC study of 39 neonates, there were another two cases (5.1%) of T21,[9] which is significantly higher percentage than the incidence of T21 overall in the general population (13.5/10,000 births).[10] These findings suggest that there may be an association of NEC with Down syndrome that may warrant further exploration.

Turner syndrome: The same study that identified two full-term neonates with T21 also found that one of the full-term neonates with NEC had Turner syndrome (2.5%).[9] In another study of 14 neonates with full-term NEC, there was one patient with Turner syndrome (7.1%). Since the incidence of Turner syndrome is 1/2500 female births, their representation in the cohorts can be considered very high. Since full-term NEC is commonly associated with congenital heart defects and Turner syndrome is associated with congenital heart disease in 23–50% of cases,[11] it is plausible that the association is indirect due to cardiovascular causes.

Relationship between Structural Chromosomal Disorders and NEC

Chromosome 1 (Chr1): A study of identical twins with identical deletions in chromosome 1 (1p32.3-p22.2: 57652246_89311711) identified a number of pathologies in both twins, including NEC that required surgery and resulted in the loss of the majority of small bowel in one of the twins.[12] Necrotizing enterocolitis in both twins was unique, as compared to other described cases of Chr1 deletions.[13–15] The various described Chr1 deletions in the four publications affected different regions of Chr1, suggesting that the particular region deleted in the twins with NEC may harbor genes whose absence may increase susceptibility to NEC. The region deleted in the twins with NEC contains 181 known genes, which were not listed in the publication, but we are providing here. Among the 181 genes, there are several that could be obvious candidates for NEC susceptibility due to their roles in inflammation, cellular differentiation, and cell death pathways, such as jun proto-oncogene (JUN), autophagy-related 4C, cysteine peptidase (ATG4C), forkhead box D3 (FOXD3), and integrin beta 3 binding protein; beta3-endonexin (ITGB3BP). While the reported cases are relatively few, the data are intriguing enough that a follow-up analysis on larger cohorts of chromosome 1 defects appears to be justified.

Chromosome 6: NEC-like intestinal necrosis had been described in two infants and in one neonate that was full-term or near full-term born by Esdal et al.[16] All three cases shared a deletion on chromosome 6 in the region 6q25.3 to q26. One of the infants had a deletion on chromosome 6, while one of the infants and the neonate were siblings and had identical unbalanced chromosome 6 to chromosome 18 translocations resulting in the loss of genetic material from chromosome 6. All three patients had severe bowel necrosis with pneumatosis intestinalis and bloody stools that required surgery. The authors noted that there were four other patients reported in the literature with similar chromosome 6 deletions, but without reported intestinal complications.[17]

The deleted chromosomal region of chromosome 6 in the three patients that had bowel necrosis contained a large number of genes (Table 2). Esdal et al. singled out ezrin (EZR), as a potential important gene among the ones that are deleted in these patients, due to its localization in intestinal epithelial cells and due to its significance in intestinal development in murine models.[18,19] Additionally, there are other genes deleted with this portion of chromosome 6, such as superoxide dismutase 2 (SOD2) and NADPH oxidase 3 (NOX3), which are critical antioxidant enzymes

Table 2: Genes within the shared deleted region arr [GRCh37] 6q25.3q26(155699183_163554531) × 1 (Adapted from Esdal et al. 2018; Table 1)

Gene symbol
NOX3, tRNA-Pseudo, LOC105378068, MIR1202, SNORD28B, ARID1B, M1R4466, TMEM242, ZDHHC14, MIR3692, AK092386, SNX9, SYNJ2, AK026758, SYNJ2-IT1, SERAC1, GTF2H5, TULP4, SNORA116, MIR7161, TMEM181, DQ586009, DYNLT1, SNORA116, SYTL3, MIR3918, EZR, AX747826, EZR-AS1, OSTCP1, C6orf9, RSPH3, TAGAP, LOC101929122, FNDC1, AK130765, MIR_633, LINC02529, BC016015, SOD2, WTAP, LOC100129519, SOC20T1, AC AT2, TCP1, SNORA20, SNORA29, MRPL18, PNLDC1, MAS1, IGF2R, AIRN, LOC729603, SLC22A1, SLC22A2, SLC22A3, LPAL2, LPA, PLG, MAP3K4, AGPAT4, AGPAT4-IT1, PRKN (PARK2), LOC105378098, PACRG, PACRG-AS2, AK058177

Sources: RefSeq and UCSC Genome Browser (ucsc.genome browser; hg19), order approximate

and Mitogen-Activated Protein Kinase Kinase Kinase 4 (MAP3K4), which is a central component of the MAPK signaling pathway that may be implicated as well.

It is similar to several other chromosomal abnormalities discussed in this article that bowel necrosis occurred in full-term or near full-term infants and a neonate, which may be viewed as a potentially strong indication that the affected region of chromosome 6 in these infants harbors genes that are relevant to NEC pathogenesis. However, two of the patients had significant cardiac abnormalities, and one of them had intestinal malrotation that had to be surgically repaired, offering the potential explanation that the bowel necrosis was caused indirectly by the chromosomal abnormality by causing conditions that may have served as underlying causes for bowel necrosis.

Chromosome 15 and Chromosome 22: There were incidental case reports of NEC being observed in neonates with 15q26.1 deletion and with 22q11 deletion syndrome.[20,21] 22q11 deletion syndrome is one of the more common chromosomal abnormalities with an incidence of ~1:4000 live births. The affected neonate was born at 40 weeks gestation and developed NEC on postnatal day 3. Although there are no other reports focusing on 22q11 deletion syndrome and NEC, it is notable that cases of NEC are sporadic in published cohorts of 22q11 deletion syndrome, which mostly consist of full-term neonates. 22q11 deletion is the most common cause of DiGeorge syndrome. In a cohort of 467 neonates with partial DiGeorge syndrome, there were 460 with 22q11 deletion and 3 cases of NEC.[22] It is unknown what the gestational ages of these neonates were at birth and at what age they were diagnosed with NEC. Deletions of the terminal region of chromosome 15 are rare and have been suggested to be potentially predisposing to congenital diaphragmatic hernia.[23,24] Beyond the single case report of NEC association with 15q26.1 deletion, we could not find additional evidence for a stronger association of chromosome 15 deletions and NEC. Therefore, the associations with 15q26.1 deletion and 22q11 deletion syndromes in these cases could well be incidental.

Conclusions

The most convincing data regarding association of chromosomal disorders with NEC is available for trisomy 21. This may be due to the fact that a very large cohort of T21 cases was studied, along with cohorts of T13 and T18, allowing a robust analysis. The other chromosomal disorders mentioned have not been studied at the same scale, and based on the sporadic publications, the evidence is intriguing but far from being conclusive. It will be worthwhile to systemically analyze the potential association of NEC with all common chromosomal disorders as such data may provide useful prognostic value.

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