Rare chromosome disorders and their developmental consequences

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Introduction

Professionals working in disability services often encounter clients who have chromosome disorders such as Williams, Angelman or Down syndromes. As chromosome testing becomes increasingly sophisticated, however, more people are being diagnosed with very rare chromosome disorders that are identified not by a syndrome name, but rather by a description of the number, size and shape of their chromosomes (called the karyotype) or by a report of chromosome losses and gains detected through an advanced process known as microarray-based comparative genomic hybridisation (array CGH).

For practitioners who work with individuals with rare chromosome disorders and their families, a basic level of knowledge about the evolving field of genetics, as well as specific knowledge about chromosome abnormalities, is essential since they must be able to demonstrate their knowledge and skills to clients (Simic & Turk, 2004). In addition, knowledge about the developmental consequences of various rare chromosome disorders is important for guiding prognoses, expectations, decisions and interventions.

The current article provides information that aims to help practitioners work more effectively with this population. It begins by presenting essential information about chromosomes and their numerical and structural abnormalities and then considers the developmental consequences of rare chromosome disorders through a critical review of relevant literature.

Chromosomes and Chromosome Abnormalities

With the exception of egg and sperm cells and erythrocytes (red blood cells), every cell in the body contains 23 pairs of chromosomes that are numbered from 1 to 22 according to their length, with 1 being the longest, plus a 23rd pair consisting of the
sex chromosomes, XX or XY (Therman & Susman, 1993; Turnpenny & Ellard, 2005). Resembling long threads, chromosomes have a short arm (referred to as p) and a long arm (q) that are joined in the middle by a centromere. The normal complement of chromosomes produces 46,XX in females and 46,XY in males. Based on chromosome banding patterns, a numbering system is used to describe regions, bands and sub-bands on chromosomes.

Occurring in 0.5 to 1% of live births, and accounting for around 50% of all spontaneous miscarriages, chromosome disorders result from the addition, deletion or rearrangement of varying amounts of chromosome material either as inherited or, more frequently, as spontaneous (de novo) events (Gardner & Sutherland, 2004; Haydon, 2008; Obe & Natarajan, 1994). Numerical anomalies involve either missing or extra whole chromosomes, while chromosome breakages can result in a range of structural disorders involving the loss or addition of varying segments of chromosome material. Duplications (sometimes referred to as partial trisomies) involve an extra copy of a chromosome segment. Deletions (also known as partial monosomies) may occur at the end of the chromosome (terminal) or a piece may be missing from some point within the chromosome (interstitial). Translocations result when the broken segments of two or more chromosomes exchange places. Such rearrangements are usually inconsequential for health and development in the carrier, provided all the chromosome material is still present in each cell and the translocation is thus “balanced”. However, there are likely to be problems with reproduction and a risk of unbalanced rearrangements occurring in future generations. Other chromosome anomalies include inversions, which result when two breakages are followed by reconnection of the intervening segment in reverse order, and rings that are formed when both chromosome tips break off and the two sticky ends fuse.
The most common chromosome disorder, Down syndrome, usually involves a third copy (trisomy) of chromosome 21 in every cell of the body. Trisomies 13 (Patau syndrome) and 18 (Edwards syndrome) are occasionally survivable, although they generally produce much more severe developmental consequences than does Down syndrome (Baty, Jorde, Blackburn & Carey, 1994). Trisomy mosaicism, in which only a proportion of cells carry the additional chromosome, has been reported for most chromosomes including 4 (Brady, May & Fernhoff, 2005), 8 (Habecker-Green et al., 1998), 12 (Staals, Schrander-Stumpel, Hamers & Fryns, 2003), 20 (Ensenauer et al., 2005), 21 (De A. Moreira, San Juan, Pereira & de Souza, 2000) and 22 (Florez & Lacassie, 2005), in some cases with no apparent detrimental effects on development.

Because they occur with sufficient frequency and because their presence results in a distinctive phenotype, some chromosome anomalies have been classified as syndromes. Among the more familiar ones are Wolf-Hirschhorn, Cri du Chat, Williams, Smith-Magenis and Velocardiofacial (and the related DiGeorge and Shprintzen-Goldberg) syndromes which involve deletions on chromosomes 4p, 5p, 7q, 17p and 22q, respectively. Turner syndrome results when only one X chromosome is present (producing the karyotype 45,X in affected females) while in males an additional copy of the X chromosome leads to Klinefelter syndrome (47,XXY). In most cases, Prader-Willi syndrome is caused by a deletion on 15q derived paternally while, intriguingly, the same deletion on the maternally derived chromosome produces Angelman syndrome. Other less familiar syndromes include Jacobsen (terminal deletion 11q) and Miller-Dieker, which involves a deletion on 17p, but at a breakpoint different from that occurring in Smith-Magenis syndrome.
There is also a wide array of less common or less distinctive chromosome disorders that occur in live births and it is these very rare abnormalities that are the focus of the current article. When diagnosed, rare chromosome disorders are given a label that correspond to their karyotype, such as “Duplication (9)(p22pter) with Deletion (11)(q23.3qter)” or “Ring (20)(p13q13.13)” rather than an actual name, making it difficult for families to communicate their child’s diagnosis to others and for service providers to categorise the disability. At times more than one chromosome abnormality is present, leading to complex karyotypes with as many as seven affected chromosomes and up to 10 separate breakpoints (Wieczorek et al., 1998). The vast number of possible anomalies and their extreme rarity and possible uniqueness sometimes lead to diagnoses that are accompanied by the pronouncement that an individual is the only known case in the world. However, as methods of testing become more advanced, more accessible and more commonly performed, it is likely that an increasing number of cases will be identified and reported in the literature.

**Developmental consequences of rare chromosome disorders**

Most case reports about rare chromosome disorders are published in the medical, rather than psychological, literature. Consequently, the focus is on genetic, medical and physical data with very little, if any, consideration given to cognitive, social-emotional and behavioural outcomes. In an analysis of case reports of trisomy 17p, for instance, Paskulin, Zen, Rosa, Manique and Cotter (2007) provided a table of 50 clinical findings, 49 of which were physical and medical features and just one developmental (specifically, neuropsychomotor delay). Only a very small number of papers feature detailed neuropsychological assessments (see, for example, Chilosi et al., 2001; McSweeny, Wood-Gottfried, Chessare & Kurczynski, 1993; Turk, Christie, Sales & Surtees, 1993).
Among reports of developmental outcomes, characteristics such as growth retardation, developmental delay, intellectual disability, delayed or impaired speech, behaviour problems and sensory deficits are frequently mentioned. Some researchers have identified phenotypic patterns that appear to be associated with certain karyotypes including 1p36 deletion (Battaglia et al., 2008; Kang et al., 2007; Okamoto et al., 2002), 6q deletion (Elia et al., 2006; Striano et al., 2006), 9p deletion (Chilosi et al., 2001; Saha, Lloyd, Russell-Eggitt & Taylor, 2007), trisomy 17p (Paskulin et al., 2007) and 18q deletion (Cody et al., 2007; Semrud-Clikeman et al., 2005). However, these studies have been based on small samples and, unlike some of the more common chromosome syndromes, typical features such as the hyperphagia seen in Prader-Willi syndrome ((Dykens, Maxwell, Pantino, Kossler, & Roof, 2007; Russell & Oliver, 2003) have not been reported.

Despite a general impression of deficits and adverse developmental outcomes, the literature also reports individuals who appear to be developing typically in some respects. For example, there are reports of average intelligence in children with deletions on 2p (Lambert & Collinson, 1990), 6p (Chen, Cherry, Hahn & Enns, 2004), 6q (Kumar, Cassidy, Romero & Schwartz, 1999), 8p (Gilmore, Cuskelly, Jobling & Smith, 2001), 11q (Carnevale, Blanco, Grether & Castillejos, 1987; Horelli-Kuitunen, Gahmberg, Eeva, Palotie & Järvelä, 1999; Ono et al., 1996), 18q (Strathdee, Zackai, Shapiro, Kamholz & Overhauser, 1995), 20p (Rovet et al., 1995), 21q (Korenberg et al., 1991) as well as ring chromosomes 2 (Lacassie, Arriaza, Vargas & La Motta, 1999), 3 (McKinley, Colley, Sinclair, Donnai & Andrews, 1991), 7 (DeLozier, Theintz, Sizonenko & Engel, 1982), 15 (Borghgraef, Fryns & van den Berghe, 1988), 19 (Hermsen et al., 2005) and 21 (Falik-Borenstein et al., 1992; Gardner, Monk, Clarkson & Allen, 1986).
Occasionally, surprising strengths are highlighted. For instance, Blennow and Bröndum-Nielsen (1990) reported that, despite moderate intellectual disability, their case with an 8p deletion displayed excellent memory skills and could speak two languages. Other authors described average abilities in isolated areas of functioning (Thompson, Peters & Smith, 1986) and savant skills (Rovet et al., 1995) in children with deletions on 18p and 20p, respectively.

Few published reports document developmental progress at more than one point in time. When available, descriptions of progress over time are usually retrospective and dependent on the recollections of families or the availability of medical records, and data about developmental outcomes are limited. Melis et al. (2006) reviewed the progress of a child with mosaic 13q deletion annually from 13 months of age for 15 years but the only developmental information across those years was a single IQ score.

In reports of developmental outcomes, conclusions are sometimes questionable. In particular, claims or inferences of intellectual disability are often unsubstantiated by psychometric data, appearing instead to be derived from anecdotal observation or speculation rather than from standardised cognitive testing (e.g., Coco & Penchaszadeh, 1978; Moreau & Teyssier, 1982; Wieczorek et al., 1998). In the absence of psychometric data, evidence of abnormal cerebral imaging is sometimes cited as sufficient grounds for presumptions of severe intellectual disability (Feenstra, van Ravenswaaij, van der Knaap & Willemsen, 2006; Vermeer et al., 2007) and at other times useful developmental descriptions are offered to support claims of developmental delay (e.g., Asai et al., 1992; Grange, Garcia-Heras, Kilani, & Lamp, 2005; Mircher et al., 2003; Sathya, Tomkins, Freeman, Paes & Nowaczyk, 1999) although interpretations are dubious at times. For example, Stalker, Gray, Bent-
Williams and Zori (2006) decided that developmental milestones such as walking at 15 months and first words at 12 months of age represented delays, when in fact both of these milestones are within normal limits. One of the children with a partial 2q duplication described by Eussen et al. (2007) as having developmental delay was reportedly functioning “at the level of a 4-year-old toddler” at the chronological age of 5 years. No assessment results were given, and no information was provided about the basis for this conclusion.

Even when psychometric data are available, they are at times reported vaguely or inappropriately, as evidenced by descriptions of “almost normal intelligence” (Kitatani, Takahashi, Ozaki, Okino & Maruoka, 1990, p.138), “severe retardation, to between 40% and 50% of normal” (Schinzel et al., 1991, p.354) and a borderline IQ of 75 that was interpreted as confirmation of an assumption of severe intellectual disability (Paz-y-Miño, Benitez, Ayuso & Sánchez-Cascos, 1990). Incorrect interpretations of IQ scores are also found. For instance, in their report of five cases with 6q deletion, Striano et al. (2006) wrongly classified IQs of 60 as representing moderate intellectual disability (cases 1 and 3), while a lower IQ of 55 was correctly referred to as mild intellectual disability (case 4). Netzer et al. (2006) claimed that their case with 18q- had ‘above average’ verbal skills, a claim that was arguably inaccurate and misleading in the light of an IQ of 74 (derived from five WAIS-R subtests) and the result of 104 on a ‘German vocabulary IQ test’.

In summary, rare chromosome disorders have been associated with a range of developmental consequences including intellectual disability, language impairments and behaviour problems. These shared characteristics may be due to the more general effects of chromosome imbalance, rather than specific anomalies. At the same time, evidence about normal intelligence in some individuals with rare chromosome
abnormalities suggests that adverse developmental outcomes are not necessarily inevitable.

These conclusions about development are, however, drawn from a relatively limited literature base that is inadequate in some respects. Because it is likely that cases with more negative developmental outcomes are being diagnosed and reported, the literature may not be accurately portraying the range of possible outcomes that are attainable. Moreover, data are usually collected at only one point in time, comprehensive assessment batteries are rare, and interpretations of results are not always rigorous. In particular, conclusions about intellectual functioning are sometimes vague or unsubstantiated.

Implications for practitioners

Clearly, the limited literature about the developmental consequences of rare chromosome disorders makes it difficult for practitioners to work effectively with this population. Most rare chromosome disorders occur, or are identified, so infrequently that their developmental course has not yet been well documented and at times it is impossible to locate a single published case matching the karyotype of an individual seen in clinical practice (Gilmore & Campbell, 2006).

Even when appropriate literature is available, the developmental data can be sparse, inadequate or inconsistent, and consequently practitioners need to search and evaluate the literature carefully and critically, with an awareness of its limitations. For example, assertions in the literature about the inevitability of certain outcomes (e.g., “mental retardation is always present” in Mircher et al., 2003, p.177) need to be examined and rejected if they are based on small samples and inadequate or non-existent psychometric data.
Practitioners should also seek sources of information beyond the academic and professional literature. Of particular value is the Unique Rare Chromosome Disorder Support Group (www.rarechromo.org) which has established a rich database containing the developmental histories of more than 6,900 individuals with a rare chromosome disorder. Their descriptive data, collected worldwide and periodically since 1984, track development across all domains including cognitive and behavioural, thus providing an exceptional resource for families and professionals. In addition, Unique and other support groups provide a range of services, advice and support, including valuable contact with other families whose children have the same, or similar chromosome abnormalities.

Because of the notable within-group variability that characterises some chromosome abnormalities, prognoses about future development need to be tentative, taking into consideration the range of possible outcomes that have been documented in the literature, as well as the unique individual, family and contextual characteristics that are also likely to influence developmental outcomes. In particular, developmental predictions need to be sensitively expressed, since the prognostic uncertainty associated with rare chromosome disorders is likely to produce significant emotional stress and anxiety for families (Lenhard, Breitenbach, Ebert, Schindelhauer-Deutscher & Henn, 2005).

There may well be grounds for being cautiously optimistic about future development and indeed, as Baty et al. (1994) have pointed out, families tend to resent early negative prognoses, irrespective of whether or not they are well-informed and well-intentioned, and to appreciate acknowledgments of their children’s strengths and accomplishments. Families may benefit from clear explanations about the cause of their child’s chromosome abnormality (e.g., an accident in cell division around the
time of conception or the inheritance of an unbalanced translocation from one parent) and guidance on how to explain their child’s diagnosis to others, particularly since the overwhelming majority of diagnoses are not associated with a syndrome name.

Finally, practitioners may have opportunities to contribute to the research literature by producing developmental case studies of individuals with rare chromosome disorders. Case studies have the potential to provide rich data about cognitive, behavioural, social, academic and personal development that can illuminate developmental processes and trajectories. Despite limited generalisability, case reports represent the only viable research methodology for karyotypes that are so truly unique that obtaining an adequate sample for systematic investigation appears impossible or unlikely. An increasing number of reports that include robust data about developmental outcomes will provide a stronger knowledge base to guide prognoses, ongoing supports and services, and specific interventions for individuals with rare chromosome disorders.
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