Cornelia de Lange, Cri du Chat and Rubinstein Taybi Syndromes

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Introduction

In this chapter we describe three comparatively rare genetic syndromes associated with intellectual disability. The rarity of genetic syndromes impacts significantly on the amount of information that is available, the likelihood that clinicians will have experience of a syndrome and the quality of advice and intervention that may be offered. This is perhaps unsurprising given the number of genetic syndromes associated with intellectual disability but is nevertheless of concern. This problem is mirrored in the volume of research on individual rare syndromes. In this respect many rare syndromes acquire the status of orphan diseases with little or no information on cognitive and behavioural phenomenology and even less on interventions. This does not however, mean that study of these rare syndromes will not be as revealing as research into more common conditions such as Autism Spectrum Disorder. Demonstrations of associations between specific cognitive impairments and social or behavioural difference and disorder in rare syndromes can usefully inform the conceptualisation of gene-brain-behaviour-environment pathways regardless of which syndrome the pathway was identified in.

The syndromes selected for review in this chapter have been chosen because although they are rare they demonstrate different pathways to behavioural outcomes, how different domains of behavioural phenotypes may be dissociated within syndromes and variability of behavioural outcome within broad classes of behaviour. The three syndromes show striking differences in their phenomenology and in doing so demonstrate the importance of careful description and conceptualisation of cognitive and behavioural features. Levels of repetitive behaviours differ across the three syndromes as does the specificity of these behaviours. Social impairment at either end of a sociability continuum is evident when comparing Cornelia de Lange and Rubinstein Taybi syndromes, with equally important clinical implications. An expressive communication deficit is shared by those with Cri du Chat and Cornelia de Lange syndromes but the cause appears quite different. Cornelia de Lange and Rubinstein Taybi syndromes both evidence age related change but in different ways. Finally, in each syndrome genetic variability of differing forms is associated with a physical and behavioural phenotype to differing degrees. These shared and unique
patterns of characteristics illustrate why the study of syndromes, regardless of their rarity, is of importance.

**Cornelia de Lange Syndrome**

**Prevalence**

Cornelia de Lange Syndrome (CdLS) was first described by Brachmann in 1916 and subsequently by Cornelia de Lange in 1933. Beck (1976), investigating CdLS in a Danish population, found a prevalence rate of 0.5 per 100,000 with no gender differences, an estimate confirmed by Beck and Fenger (1985) for the years 1967-1982. Beck suggests that the findings are likely to demonstrate minimum figures due to problems associated with diagnosis and Opitz (1985) has proposed that a birth prevalence of approximately 1 per 10,000 is more accurate. With the identification of a more mild phenotype it is increasingly likely that the prevalence will be higher than 1 per 50,000.

**Physical Characteristics**

Common physical characteristics of people with CdLS include low birth weight, growth retardation, upper limb abnormalities, excessive hair growth and a small head circumference (Ireland, Donnai & Burn, 1993; Jackson, Kline, Barr & Koch, 1993; Kline, Stanley, Belevich, Bridsky, Barr & Jackson, 1993; Kline, Krantz, Sommer, Kliewer, Jackson, FitzPatrick, Levin & Selicorni, 2007a). Distinctive facial characteristics, considered important diagnostic features, include confluent, arch-shaped eyebrows, thin down-turned lips, long eyelashes, a low hair line, low set ears and a long philtrum (Ireland et al., 1993; Jackson et al., 1993; Kline et al., 1993; Kline et al., 2007a).

Health problems and sensory deficits are common in people with CdLS. Gastrooesophageal reflux and other gastrointestinal disorders are prominent (Luzanni et al., 2003; Hall, Arron, Sloneem & Oliver, 2008) with reports of an association between reflux and behavioural disorder including self-injury (Luzanni et al., 2003; Moss, Oliver,
Hall, Sloneem, Arron & Petty, 2005). Other health problems include heart and kidney malformations in approximately 40% (Selicorni, Sforzini, Milani, Cagnoli, Fossali & Bianchetti, 2005), dental problems, otitis media (Hall et al., 2008; Kline et al., 2007b; Marchisio et al., 2008) and ophthalmic and orthopaedic disorders (Levin et al., 1990; Nallasamy et al., 2006; Roposch et al., 2004; Wygnanski-Jaffe et al., 2005). Health problems are related to low mood (Berg et al., 2007) and warrant repeated assessment with aggressive intervention. Sensorineural hearing loss is reported with loss of or compromised neural function evident in 20%, conductive hearing loss due to middle ear effusion is also reported in 60% of individuals. This hearing loss may contribute to the delayed onset of speech and is correlated with severity of intellectual disability (Marchisio et al., 2008). Slow peripheral nerve transmission speeds have been recorded (Oliver, Jephcott, Seri, Friess, Kline & Moss, 2007) and may be related to anecdotally reported high pain thresholds.

**Diagnosis and Genetic Studies**

The first genetic mutation was mapped to 5p13.1 the site of the NIPBL gene (Krantz et al., 2004; Tonkin, Wang, Lisgo, Bamshad & Strachan, 2004). NIPBL is the human homolog of the Drosophila Nipped-B gene. The exact function of the human NIPBL gene product, delangin, is unknown. To date, NIPBL mutations have been identified in between 20 and 50 percent of those diagnosed with CdLS cases (Gillis et al., 2004; Krantz et al., 2004; Miyake et al., 2005; Tonkin et al., 2004). Some studies have identified a difference between those individuals with and those without the mutation with regard to stature, degree of disability and presence of limb abnormalities (Gillis et al., 2004; Miyake et al., 2005). However, these findings need to be confirmed.

Subsequent to the discovery of the mutation of the NIPBL gene, additional mutations of the SMC3 gene on chromosome 10 (Deardorff et al., 2007) and X linked SMC1 gene (Musio et al., 2006) have been identified and are reported to account for 5% of cases. All three genes are involved in the structure and regulation of the cohesin complex (Liu & Krantz, 2008). In total these three gene mutations still only account for approximately
55% of those diagnosed with CdLS, consequently it is likely that further gene mutations will be discovered. Recently, a knock out mouse model of the NIPBL mutation has been described with features similar to those observed in CdLS including small size, craniofacial anomalies, heart defects, hearing abnormalities, microbrachycephaly and behavioural disturbances, particularly stereotyped circling behaviour (Kawauchi et al, 2009).

**Intellectual disability**

CdLS was thought initially to be always associated with severe intellectual disability (Ptacek et al., 1963). However, a number of case studies report intelligence scores in the mild intellectual disability and normal range (Moeschler & Graham, 1993; Stefanatos & Musikoff, 1994). It is now recognised that the range of IQ scores seen in CdLS is wide, although most individuals diagnosed with CdLS do have intellectual disabilities (Hawley et al., 1985).

Surveys of the range of intellectual disability indicate that most individuals have moderate to profound intellectual disabilities. Beck (1987) used the Vineland Social Maturity Scale to assess psycho-social skills in thirty-six individuals with CdLS. Social Quotients indicated that 50% of participants had profound disabilities, 14% had severe, 17% moderate, 6% had mild intellectual disabilities and 14% of participants scored within the borderline or normal range. These figures are supported by a postal survey of 49 children and adults with CdLS with 43% of participants showing profound intellectual disabilities, 20% severe, 18% moderate, 8% mild and 10% borderline disabilities (Berney, Ireland, & Burn, 1999). Oliver et al. (2008) using the Vineland Adaptive Behavior Scales report 50% of individuals with CdLS to have a profound intellectual disability this figure was 24, 15 and 11 for severe, moderate and mild respectively. An extensive study of development in CdLS using formal IQ testing has shown that the mean intelligence test score in people with CdLS falls within the moderate intellectual disability range (Kline et al., 1993). Results from the standardised tests indicated within participant strengths in the areas of perceptual organisation and visuo-spatial memory,
recorded by scores of up to three standard deviations higher than in other domains. The cognitive profile of CdLS warrants further research.

**Communication**

Prevalence figures of individuals with CdLS who do not develop speech are highly variable across a number of studies, with reports ranging from 30-85% (Beck, 1987; Goodban, 1993; Johnson, Ekman, Friesen, Nyhan & Shear, 1976; Sarimski, 1997). This variability is likely to reflect an increase in the number of mildly affected individuals being identified. Approximately 70% of individuals with CdLS display communication skills under the age equivalent of three years, 44% of individuals aged over two years are able to combine two or more words and only 4% develop language skills in the normal range (Beck, 1987; Goodban, 1993). These findings indicate that speech is compromised and when evident might develop later than expected. Using the Pre-Verbal Communication Scale (PVCS; Kiernan & Reid, 1987) Sarimski (1997) reports that only 11% of 27 individuals used conventional words, suggesting that Goodban’s findings might be an overestimate of the frequency of verbal communication. In addition to a delay in expressive communication, Goodban (1993) also states that expressive communication is notably inferior to the comprehension of language. Kline et al. (1993), report similar results and this observation was confirmed in a case control study by Oliver et al. (2008) using the communication subdomain scores of the Vineland Adaptive Behavior Scale.

Interestingly, Sarimski (2002) has demonstrated that the mean frequency of non-verbal communicative acts is significantly lower in individuals with CdLS compared to individuals with Cri du Chat (CdC) and Down syndromes (DS). According to Basile, Villa, Selicorni and Molteni (2007), fourteen out of 56 individuals with Cornelia de Lange syndrome aged between one and 31 years showed no verbal or non-verbal acts of intentional communication. These findings suggest that both verbal and non-verbal communication skills are compromised in CdLS. However, non-verbal communication is not completely absent. Sarimski (1997) reported the use of non-verbal communication to
get other people’s attention and to indicate needs. Similar results are described by Oliver, Arron, Hall, Sloneem, Forman and McClintock, (2006). These findings suggest that rather than demonstrating socially directed communication, communication in Cornelia de Lange syndrome is largely restricted to personal demands. This lack of socially directed communication is also evident in individuals who do develop expressive communication skills. Anecdotally, it has been reported that those individuals who do develop speech are often reluctant to use their communication (Goodban, 1992). Johnson et al. (1976) reported that although two out of nine participants had developed speech, both of them were quiet and spoke very little. Moss, Oliver, Wilkie, Berg, Kaur and Cornish (2008), anecdotally report a reluctance to communicate in their study. Selective mutism appears to be common and an experimental study by Richards, Moss, O’Farrell, Kaur and Oliver (2008) has demonstrated anxiety related behaviours at the point of social engagement in ongoing social interactions.

**Social interaction**

Johnson et al. (1976) describe a ‘paucity of social response’ in seven out of nine participants with CdLS. More recently, several studies have provided evidence to suggest that Johnson et al.’s (1976) proposal of compromised social interaction skills in CdLS may have been accurate. According to Sarimski (1997) 50% of individuals with Cornelia de Lange syndrome have ‘abnormal’ eye contact and 54% were described by parents as being ‘isolated as if in their own world’. Sarimski also described a lack of appropriate facial expression with 48.1% of parents reporting difficulty in recognizing their child’s feelings. Collis, Moss, Jutley, Cornish and Oliver (2008) report lower levels of facial expression of positive affect in CdLS. Oliver et al. (2006) also described a high prevalence of socially avoidant behaviors such as ‘wriggling out of physical contact’ and ‘attempting to move away during an interaction’ in fourteen out of sixteen individuals with CdLS. Further detailed study of early social interaction skills has demonstrated that poor eye contact in the first year of life may be predictive of social relatedness in later years (Sarimski, 2007). Interestingly, Sarmiski reported that 46.2% of individuals with CdLS were over-friendly with strangers. This indicates that some individuals with
Cornelia de Lange syndrome do engage in social interaction although their understanding of what this involves might be limited.

**Autism Spectrum Disorder**

A number of studies have demonstrated that CdLS is associated with autism spectrum disorder like impairments including poor expressive communication skills, social deficits, repetitive behaviours and a preference for rigid routines (Bay, Mauk, Radcliffe & Kaplan, 1993; Beck, 1987; Goodban, 1993; Hyman, Oliver & Hall, 2002; Johnson et al., 1976; Sarimski, 1997). Several studies have reported a heightened probability of autism in affected individuals. Using a revised version of the Autism Behavior Checklist (Krug, Arick & Almond, 1980), Berney et al (1999) report that 53% of 49 participants with CdLS showed the combination of impaired social interaction and communication skills and the presence of repetitive behaviour to a degree that might suggest the presence of autism (pronounced in 37% and mild in 16%). Similar findings are reported by Bhuiyan et al. (2005) who demonstrate that seventeen out of nineteen individuals with CdLS scored at a similar level to that expected in individuals with autistic spectrum disorder on the Diagnostic Interview for Social and Communication Disorders (Wing, 2002). On the autistic relating subscale of the Developmental Behaviour Checklist (Einfield & Tonge, 1995), fifteen of the nineteen participants scored at a similar level to that expected in individuals with autistic spectrum disorder. Using the Autism Diagnostic Observation Schedule, Moss et al. (2008) demonstrated that 61.8% of individuals with CdLS score above the cut-off for autism compared to 39.7% of individuals with Cri du Chat syndrome (CdCS). These groups were comparable for degree of disability and receptive language skills. Specifically, the CdLS group evidenced a greater level of impairment on the communication domain of the assessment in comparison to the CdCS group. This difference was replicated using the Social Communication Questionnaire, and was not accounted for by degree of disability, receptive language skills or the difficulties of identifying autism in individuals with profound intellectual disability. Finally, Oliver et al. (2008) reported that 32.1% of 54 individuals with CdLS scored within the ‘severe autism’ category of the CARS compared to only 7.1% of a matched control group of
individuals with intellectual disability, suggesting that the relationship between CdLS and ASD is not solely accounted for by associated degree of disability. Oliver et al. (2005) also report that those with CdLS scored significantly higher on the Autism Screening Questionnaire (Berument, Rutter, Lord & Pickles, 1999) than individuals with Cri du Chat and Prader-Willi syndromes, with a mean score comparable to that of a group with Fragile X syndrome. In combination, these findings indicate that features of ASD are evident in CdLS at a level similar to that seen in a syndrome considered high risk for ASD and that these features are independent of degree of intellectual disability.

**Repetitive behaviour and restricted interests**

Johnson *et al.* (1976) found seven out of nine (78%) individuals with CdLS to show stereotyped behaviour, with topographies including hand posturing, hand regard, body twirling and body turning. In a postal survey of 88 individuals with CdLS, 57% had shown stereotyped behaviour in the last month (Hyman et al., 2002) and Sarimski (1997) used the Behavior Problems Inventory to assess the presence of five topographies of stereotyped behaviour in 27 individuals with CdLS. The most common topographies included body rocking (56% of participants), bizarre body positioning (52%) and turning objects (44%). Comparative figures for individuals with intellectual disability range from 54 to 80% suggesting that the prevalence of stereotyped behaviour in general intellectual disability populations are similar to those seen in CdLS In a detailed study of repetitive behaviour across syndromes Moss, Oliver, Arron, Burbidge and Berg (2009) showed that individuals with CdLS demonstrate significantly more tidying up and lining up behaviours than at least two other syndrome groups.

Hyman et al. (2002) report that 87.5% of affected individuals engage in at least one form of compulsive like behaviour. Ordering and checking compulsions were the most common forms and a greater number of compulsive behaviours were reported within older participants. Comparative figures for individuals with severe and profound intellectual disabilities using the same measure have demonstrated that compulsions are shown by 40% of individuals in this population. Oliver et al. (2008) demonstrated that
individuals with Cornelia de Lange syndrome display significantly more compulsive behaviour than a comparison group of individuals matched on a number of demographic variables, including degree of disability and that this difference could not be accounted for by the presence of autistic spectrum disorder.

**Self Injurious Behaviour**

Although results have varied, research examining self-injury in children and adults with CdLS suggests higher prevalence rates (ranging from 16% to 64%) for self-injurious behaviour within CdLS (Beck, 1987; Berney et al., 1999; Gualtieri, 1990; Hyman et al., 2002; Sarimski, 1997). In a case-control study Oliver et al. (2009) reported a prevalence of 55.6% which was not statistically significantly higher than that for a matched contrast group (41.3%). This suggests that whilst the prevalence of SIB is high in CdLS it does not fulfil the definition of a component of a behavioural phenotype.

Topographies of self-injurious behaviour reported in the early literature did not indicate a distinct topography associated with CdLS. Gualtieri (1990) reported that the most common topographies of self-injury include biting (shown by 27% of individuals), hitting (20%), hair pulling (15%), head banging (11%) and picking (10%). Berney et al. (1999) also found that finger biting and head banging was common in CdLS. In a recent case control study Oliver et al. (2009) described higher levels of more mild forms of self-injury. During natural observations Sloneem et al. (2009) report higher levels of biting and more self-injury directed toward the hands.

Self-injurious behaviour within CdLS has often been described as severe. Bryson et al. (1971) and Dosseter et al. (1991) present case studies on individuals with CdLS causing significant injury to themselves resulting in repeated infections, excessive bleeding and loss of tissue and requiring stitching and hospitalisation. Restraints and protective devices are also commonly required to manage self-injury in CdLS and the 38 to 40% prevalence rate for the use of restraints reported in the literature (Berney et al., 1999; Gualtieri, 1990) is three times that seen in general intellectual disability populations.
Individuals also express a preference for wearing restraints and a fear of being without restraints (Dossetor et al., 1991; Shear et al., 1971). Incorporating a measure of self-restraint, Hyman et al. (2002) found that 53% of participants displayed at least one form of self-restraint with a significant association between self-injury and self-restraint. A number of authors have also suggested that self-injurious behaviour in CdLS has a “compulsive quality” (Bryson et al., 1971; Shear et al., 1971). Hyman et al. (2002) demonstrated that compulsive behaviour was associated with self-injury and self-restraint.

Intervention, experimental and natural observation studies on self-injury in CdLS have shown that the environment can influence and shape behaviour in CdLS. Three separate studies have demonstrated the effect of environmental variables such as adult attention on the expression of self-injury and the effectiveness of behavioural treatment programmes in reducing the self-injury shown by three children with CdLS (Bay et al., 1993; Menolascino, McGee & Swanson, 1982; Singh & Pullman, 1979). The data from these three studies support the notion that self-injury in individuals with CdLS can be influenced by factors in the environment. However, common problems observed with each of these studies are the use small sample sizes and the reporting of only positive cases. Using larger samples of individuals with CdLS, Moss et al. (2005), Oliver et al. (2006) and Sloneem et al. (2009) all showed an association between environmental events and self-injury in a proportion of participants with CdLS.

Detailed observations of individuals with CdLS have shown that those who self-injure may seek restraint and that distress is evident when physical restraints are removed (Dosseter et al., 2001; Shear, Nyhan, Kirman & Stern, 1971). Hyman et al. (2002) found that 53% of individuals with CdLS showed at least one form of self-restraint. The most common forms included holding onto other people to seek restraint, holding or squeezing objects, wrapping in clothing and holding hands together. The association between SIB and self-restraint was significant and those individuals showing SIB and self-restraint were also significantly more likely to display compulsions, suggested that for some
individuals with CdLS self-injurious behaviour may become difficult to control and regulate.

**Physical Aggression**

Hyman *et al.* (2002) found that 43% of individuals with CdLS had shown physical aggression in the last month and in a study by Gualtieri (1990) 41% of 138 participants had shown physical aggression during the course of their lives. Berney et al. (1999) found a prevalence rate of 10% in a sample of 49 individuals for daily physical aggression. Hyman et al. (2002) report prevalence figures of 53% for destruction of property, Berney et al. (1999) found 33% of participants to show aggression towards objects, and Gualtieri (1990) reports destructiveness in 10% of individuals with CdLS. In the observational case control study by Sloneem et al. (2009) aggregated ‘other challenging behaviour’, which included aggression and destruction of the environment, was reported to be significantly lower in the CdLS group than that seen in a matched contrast group.

**Hyperactivity**

Berney *et al.* (1999) found that 74% of children and adults with CdLS displayed at least one of four symptoms of hyperactivity, including having an attention span of less than ten minutes, “fidgetiness”, “chaos creating” activity and over-activity and Gualtieri (1990) reports hyperactivity in 13% and non-compliance in 10% of individuals with CdLS. In a clinical sample of individuals with CdLS, Greenberg and Coleman (1973) found hyperactivity in 64% of participants, although it is not clear how behaviour was measured in the study. In the Luzanni et al. (2003) study hyperactivity was reported to be related to gastro-oesophageal reflux.

**Conclusions**

Health problems are very common in CdLS and impact significantly on well being and behaviour. Regular assessment with appropriate intervention should be of high priority.
The majority of individuals with CdLS fall within the mild to profound range of intellectual disability. There are deficits evident in communication skills compared to overall ability with a discrepancy between expressive and receptive language skills. Expressive language delay is common and hearing impairments should be treated at the earliest opportunity.

An increasing number of studies have investigated the association between CdLS and autism spectrum disorder. Individuals with CdLS are often described as showing poor social skills and “disliking” social contact, showing communication deficits, excessive shyness and selective mutism and displaying specific forms of repetitive behaviour. More recent studies have highlighted that a heightened probability of autism spectrum disorder is evident but the nature of the impairments and the relationship with autism spectrum disorder warrants further research.

Prevalence rates for topographies of challenging behaviour including self-injury, aggression and hyperactivity in CdLS are high but case control studies reveal that SIB is no more common than might be expected when degree of intellectual and physical disability are controlled for and aggression and destruction of the environment are less common than expected. Several studies of the severity of self-injurious behaviour have indicated that when individuals with CdLS show self-injury, they can cause significant harm. This observation is supported by data that show that self-injury is associated with self-restraint and compulsive behaviour. Additionally, self-injury appears to be associated with pain and discomfort that result from the health conditions associated with CdLS. Observational and intervention studies have shown that self-injury can be associated with environmental events, suggesting that for a proportion of people behavioural approaches might be effective. Assessment and intervention protocols for self-injury and other challenging behaviours in CdLS are available in Oliver et al. (2003) and Oliver et al. (2009).

**Cri du Chat Syndrome (5p deletion syndrome)**
Prevalence

First described by Lejeune in 1963, CdCS (CdCS), which takes its name from the ‘cat-like cry’ is often referred to as Deletion 5p- syndrome and chromosome five short arm deletion. The prevalence has been estimated at 1 in 50,000 live births and although the exact gender ratio is unknown, the syndrome is thought to be approximately twice as prevalent in females as in males (Niebuhr, 1978; Van Buggenhout et al., 2000; Dykens, Hodapp and Finucane, 2000).

Physical characteristics

The distinctive cat-cry is a core feature of the syndrome and is still regarded as an important early clinical diagnostic feature in most but not all individuals (Mainardi et al.2006). The cry is thought to be caused by anomalies of the larynx (small, narrow and diamond shaped) and of the epiglottis that is usually small and hypotonic (Neibuhr, 1978). Many infants tend to be of low birth weight and low weight usually persists in the first two years of life for both sexes (Marinescu et al., 2000). Feeding difficulties are common and the associated failure to thrive may be the initial clinical presentation. Some infants may require tube feeding, a process which may have to continue for several years. Gastroesophageal reflux is common in CdCS during the first years of life (Collins & Eaton-Evans, 2001). Other health problems include respiratory tract infections, otitis media and dental problems. Many individuals with CdCS are prone to developing a curvature of the spine (congenital scoliosis) and this can become more apparent with advancing age. Some of the most frequently cited physically defining features of CdCS are facial characteristics including microcephaly, rounded face, widely spaced eyes, downward slanting of palpebral fissures, low set ears, broad nasal ridge and short neck (Dykens et al., 2000; Goodart et al., 1994; Gersh et al., 1995; Marinescu et al., 1999). Studies indicate that facial features change over time, specifically, lengthening of the face and coarsening of features (Mainardi et al. 2006).

Diagnosis and Genetic Studies
CdCS is predominantly caused by a partial deletion on the tip of the short-arm of chromosome 5 (with a critical region of 5p15). The size of the deletion ranges from the entire short arm to the region 5p15 (Overhauser et al., 1994). A de novo deletion is present in 85% of cases; 10 to 15% are familial with more than 90% due to a parental translocation and 5% due to an inversion of 5p (Van Buggenhout et al., 2000). Neibuhr first identified the specific chromosomal region implicated in the syndrome as 5p15.1-5p15.3, using cytogenetic analysis (Niebuhr, 1978). More recent work has mapped specific critical areas within this region as being responsible for the expression of the core clinical features of the syndrome. For example, the characteristic high pitched ‘cat-like’ cry from which the syndrome derives its name has been mapped to the proximal part of 5p15.3 (Gersh et al., 1995), the speech delay to the distal part of 5p15.3 and severe intellectual impairment to 5p15.2 (Overhauser et al., 1994). This distinctive cry is considered the most prominent clinical diagnostic feature of the syndrome (Mainardi et al. 2006). Though relatively rare, CdCS represents the most common deletion syndrome in humans (Cornish, Bramble and Standen, 2001).

**Intellectual disability**

Early reports on CdCS suggested that profound intellectual disability was a common feature of the syndrome (Niebuhr, 1978). More recent, albeit limited, research data indicate that there is a wider range of cognitive ability (Cornish, 1996; Cornish, Bramble, Munir & Pigram, 1999). Progression in motor development is delayed and adaptive behaviour within the domains of socialisation, communication, daily living skills and motor skills does not appear to show any significant strengths or weakness, although no contrast groups have been employed in research studies (Cornish, Munir & Bramble, 1998). Marinescu et al. (1999) found no association between the size of the genetic deletion on 5p and scores on the Vineland Adaptive Behavior Scales (Sparrow, David & Cicchetti, 1984). However, individuals with translocations have been found to have a more severe developmental delay, heightened social withdrawal and more autistic-like
features than those with deletions (Dyckens & Clarke, 1997; Mainardi et al. 2006; Sarimski, 2003).

**Communication**

Most individuals with CdCS have minimal or no speech (Cornish et al., 1999) while receptive language tends to be significantly more developed than expressive and written skills. According to Sohner and Mitchell (1991) indicators of compromised expressive communication are present prior to speech development and can be evidenced by a delayed pattern of babbling development during infancy. Some researchers have suggested that the delay in the development of verbal communication is a result of congenital abnormalities of the larynx and delay in motor skills. It seems likely that problems in expressive language in CdCS are related to the physical abnormalities in the larynx and delayed motor skill development (Manning, 1977; Neihbur, 1978; Sohner & Mitchell, 1991). Receptive language skills are considered a marked strength within the cognitive profile of CdCS (Cornish et al., 1998; Cornish & Munir, 1998).

Whilst language development is significantly delayed, a number of studies have demonstrated that there is potential for verbal and non-verbal communication to develop in affected individuals. Wilkins, Brown and Wolf (1980) reported that of 65 individuals with CdCS, 16.9% had a vocabulary of more than 100 words and were able to form sentences of three or more words. A further 36.9% had limited but useful single word vocabularies. According to Cornish and Pigram (1996) only 25.9% of 27 individuals with CdCS used speech to communicate their needs while 55% were able to communicate using non-verbal methods. Importantly, Sarimski (2002) has demonstrated that in addition to using verbal and non-verbal communication to indicate their needs, individuals with CdCS engage in significantly more *socially directed* communication than individuals with Cornelia de Lange syndrome, performing at a level that is similar to individuals with Down syndrome. However, Cornish and Pigram (1996) report that only 7.4% of individuals use any formal signs, the majority (48.1%) use idiosyncratic gestures. These findings demonstrate a clear capacity and motivation to engage in communication
in individuals with CdCS and stress the importance of early intervention and introduction of sign language in order to further encourage the development of communication in individuals with CdCS.

**Social interaction**

Social interaction skills are considered to be a relative strength of individuals with CdCS (Carlin, 1983), who are often noted to have a ‘friendly and happy’ demeanour. However, empirical evidence for this is inconsistent. In a sample of twenty individuals with CdCS, no significant differences were identified between scores on the socialisation domain of the Vineland Adaptive Behavior Scales (Sparrow et al., 1984) compared to communication, motor and self help domains (Cornish et al., 1998). These scores were in line with global mental age equivalence scores. Using the same assessment with a larger sample of 100 individuals with CdCS, Dykens, Hodapp and Rosner (1999; cited in Dykens et al., 2000) demonstrated that scores on the socialisation domain were significantly higher than those on the remaining three domains. Specifically, Dykens et al. (1999) report that over 80% of individuals with the syndrome show an interest in their peers and the actions of other people.

**Autism Spectrum Disorder**

Autism Spectrum Disorder like behaviours are not commonly reported in CdCS. Moss et al. (2008) used the Autism Diagnostic Observation Schedule to assess 23 children and found a prevalence rate of 31.4% for autism and 60.7% for Autism Spectrum Disorder. These rates were 0 and 8.7% respectively for scores on the Social Communication Questionnaire (Rutter et al., 2003). The prevalence of autism in CdCS reported in this study is well within the range reported for the wider intellectual disability population (up to 40%), suggesting that there is not a strong association between autism and CdCS. The heightened proportion of individuals scoring above the cut off for autism spectrum disorder is likely to be accounted for by the associated intellectual disability and the
difficulties in identifying autism spectrum disorder in individuals with severe to profound intellectual disability (Moss and Howlin, 2009).

**Sleep problems**

Few studies have extensively evaluated sleep problems in CdCS, however, a small number of research studies and anecdotal reports suggest that sleep difficulties are a significant problem in this group. Cornish and Pigram (1996) reported that 30% of 20 children with CdCS had an irregular sleep pattern. In a larger study, Cornish et al. (2003) reported that sleep problems were reported by parents to be a severe cause of concern in 50% of individuals. More recently, Maas et al. (2009) reported that nine out of 30 (30%) individuals with CdCS fulfilled criteria for either a mild or a severe sleep problem. Analysis of specific behaviours related to sleep disturbance demonstrated that ‘head banging during sleep or when going off to sleep’, ‘needs security object’, ‘gagging or choking’ and ‘appears more active during daytime than other individuals’ occurred significantly more often in the CdCS group compared to individuals with Down syndrome.

**Repetitive behaviour and restricted interests**

Repetitive behaviours are generally less common in CdCS than in other genetic syndromes. However, Moss, Oliver, Arron, Burbidge and Berg (2009) report that an attachment to specific objects is a marked characteristic of the syndrome. Occurring at a clinically significant level in over 67% of individuals, the frequency of this behaviour is significantly higher in CdCS than in four other genetic syndromes including Angelman, Cornelia de Lange, Fragile X and Prader Willi syndromes and in comparison to individuals with intellectual disability of heterogeneous cause. This behaviour differs from that commonly seen in autism spectrum disorder as it is usually focussed on one specific item (as opposed to a class of items) and the item may change over time. Additionally, the behaviour tends to become less marked with age.
**Self-injurious behaviour**

Although self-injurious and aggressive behaviour appear to be common behavioural features of CdCS (Collins & Cornish, 2002; Cornish et al., 1998; Cornish & Pigram, 1996; Dykens & Clarke, 1997), there are very few studies examining prevalence and phenomenology. Using a questionnaire study to examine the prevalence of self-injury in children and young adults, Collins and Cornish (2002) found that 92% of the sample (n = 66) exhibited some form of SIB. Other questionnaire studies have found prevalence rates of self-injury to be approximately 70% (Cornish & Pigram, 1996; Dykens & Clarke, 1997). Collins and Cornish (2002) found the most common forms of SIB to be head banging, hitting the head against body parts and self-biting. In a recent questionnaire study, Arron et al. (in review) found SIB to be present in 76.8% of their sample and common topographies included pulling self, hitting self with objects, hitting self with body and rubbing or scratching self.

**Physical aggression**

Cornish and Pigram (1996) found the prevalence of aggressive behaviour in a sample of 27 individuals with CdCS to be 52%. Collins and Cornish (2002), found a higher occurrence with 88% of the sample exhibiting aggressive behaviour and the most common topographies were hitting, pulling hair, biting and pinching. Arron et al. (in review) found aggressive behaviour to be present in 70% of the sample, with an odds ratio of 2.7 compared to a matched contrast group. Currently, there are no observational studies that have examined challenging behaviour in CdCS. In addition, there are no studies that have examined the correlates of challenging behaviour in CdCS even though the syndrome is known to be associated with some risk markers for the development of challenging behaviour (e.g. severe level of intellectual disability, expressive communication impairments).

**Hyperactivity**
Hyperactivity is a commonly reported feature of CdCS. Findings vary from reports of no increase in level of activity (Baird, Campbell, Ingram and Gomez, 2001) to 90% prevalence rates of hyperactivity (Cornish, Munir & Bramble 1998) with clinical hyperactivity (ADHD) reported to be more prevalent in CdCS than in an intellectual disability comparison group (Cornish & Bramble, 2002). Of the studies assessing behaviour empirically, only two studies incorporated rating scales (Aberrant Behavior Checklist) normed on a population of people with intellectual disabilities (Dykens & Clarke, 1997; Clarke & Boer, 1998) and the most frequently used measure, although not consistently (in its entirety), was the Vineland Adaptive Behaviour Scales (VABS, Sparrow et al., 1984) on which ‘overly active’, ‘poor concentration and attention’ and ‘too impulsive’ are individual items within the Externalising Behaviour factor. Only two studies have included comparison groups of different genetic syndromes and data from other studies of community and institutionally residing individuals (Clarke & Boer, 1998) and published normative data from two heterogeneous groups (Dykens & Clarke, 1997) reducing comparable data.

The available literature documents the contrast between high prevalence of Attention Deficit Hyperactivity Disorder (ADHD) and the commonly identified immobility and severe motor delay (Cornish and Bramble, 2002). The reported high prevalence of ADHD like phenomena has raised concerns regarding both the restrictions this may place on cognitive and emotional development (Cornish et al., 1998) and its role in determining familial stress (Cornish and Bramble, 2002). This highlights a need to clarify prevalence as recommendations are being made for a relatively low threshold for medication in treating hyperactivity in these individuals (Dykens & Clarke, 1997) even though there is some evidence identifying intensive behaviour modification as the most effective intervention (Wilkins et al., 1983).

**Conclusions**

CdCS is characterised by notable variability largely determined by the position and size of the deletion on the short arm of chromosome 5. There are a number of physical
disorders and health problems that impinge on speech production and early feeding problems that warrant investigation and treatment. Scoliosis may increase with age.

Self-injurious and aggressive behaviour can be problematic and the prevalence is high for both these behaviours. There is anecdotal evidence that these behaviours may be related to an interaction between the compromised expressive language and impulsivity Oliver et al. (2009). An inability to produce speech clear enough to be understood may combine with an aversion to delay for reinforcement to evoke episodes of self-injurious or aggressive behaviour. If this analysis is correct then a combination of implementing augmentative communication systems and behavioural management might be effective. Sleep problems in CdCS also warrant investigation as this can act as a significant source of stress for families and can also impinge on daytime alertness and thus compromise educational opportunities.

The attachment to objects seen in CdCS is striking because the level of other repetitive behaviours is generally low. This profile of an isolated for of repetitive behaviour is unusual and warrants more detailed description and analysis.

**Rubinstein-Taybi Syndrome**

**Prevalence and Diagnosis**

Rubinstein-Taybi syndrome (RTS) was first described by Rubinstein and Taybi in 1963. Although prevalence estimates have varied it is thought that the most accurate estimate is approximately 1 in 125,000 live births (Hennekam, Stevens & Van de Kamp, 1990a). However, as the syndrome is diagnosed primarily by clinical characteristics it is possible that a mild presentation may be undiagnosed. The syndrome affects males and females equally (Hennekam et al. 1990a) and has been reported in all racial groups although diagnosis may be more difficult when the individual is non Caucasian due to a less marked facial expression (Rubinstein, 1990).
Genetic Studies

RTS is a multiple congenital anomaly syndrome. The first genetic anomaly identified were breakpoints, mutations and microdeletions within chromosome 16p13.3 (Lacombe, Saura, Taine & Battin, 1992). Following this discovery, Petrij et al (1995) reported a molecular analysis that highlighted a gene located on chromosome 16p13.3 that coded for the cyclic AMP response element binding protein (CBP). It was shown subsequently that, in addition to the chromosomal rearrangements of chromosome 16, RTS can also arise from heterozygous point mutations in the CBP gene itself. More recently, the E1A Binding Protein, P300 has also implicated in the syndrome (Roelfsema et al. 2005). P300 is located at 22q13.2 and is a homolog of CBP. Both are highly related in both structure and function and consequently mutations in p300 can also result RTS.

Despite these findings, chromosomal or molecular abnormalities are only found in around 55% of those diagnosed (Hennekam, 2006) and diagnosis is still based largely on the identification of clinical characteristics. At present, reports suggest that clinical differences between those diagnosed with the syndrome with and without deletions are minimal (Bartsch et al. 1999).

Physical Characteristics

The physical characteristics associated with RTS have been well documented and include broad thumbs and toes, postnatal growth retardation, small head, excessive hair growth and dental abnormalities (Hennekam & Van Doorne, 1990; Hennekam, Van Den Boogaard, Dijkstra, & Van de Kamp, 1990; Partington, 1990; Rubinstein, 1990; Stevens, Carey & Blackburn, 1990a; Stevens, Hennekam & Blackburn, 1990b).

The classical facial appearance in RTS is also well documented. Descriptions typically include a prominent ‘beaked’ nose, eyes with downward slanting palpebral fissures, long eyelashes, thick eyebrows, and a small mouth (Hennekam, 2006; Hennekam, Van Den
Boogaard, Sibbles & Spijker, 1990b; Rubinstein, 1990; Stevens et al. 1990a; Wiley, Swayne, Rubinstein, Lanphear & Stevens, 1990). Allanson (1990) reviewed those with the diagnosis of various ages and provided evidence for a changing facial phenotype. In newborns, characteristics include a prominent forehead, upward slanting palpebral fissures and a straight nose with upturned tip and fleshy bridge. Over time, palpebral fissures change to a downward slant, the nose becomes more prominent, narrow and sharp and facial asymmetry becomes more common.

Health and medical difficulties are common in RTS. Feeding and related weight difficulties have been reported repeatedly in the literature. During infancy, feeding difficulties include poor appetite, vomiting and failure to thrive (Hennekam et al. 1990b). However, a study by Stevens et al (1990b) shows poor weight gain does not persist and reports that school age boys and adolescent girls tend to be overweight for their height. Furthermore, they noted that several individuals had vigorous appetites. Consequently, comparisons regarding weight gain have recently been made between some individuals with RTS and individuals who have Prader-Willi syndrome (Hennekam, 2006).

Other health problems include renal abnormalities, constipation, vertebral anomalies, (Rubinstein, 1990), recurrent upper respiratory infections, undescended testes in males, and keloids (Hennekam, 1990). Importantly, it has been documented that individuals with RTS may suffer an increased risk of developing cancer (Hennekam, 2006). Therefore, attention to early symptoms indicative of tumours is important to ensure early intervention. In addition, studies have reported a high incidence of bone fractures in the group (Hennekam et al, 1990b; Rubinstein, 1990). It has been suggested that the cause of this may be the combination of slender bones and hypotonia with the unsteady stiff gait common in the syndrome (Hennekam et al 1990b).

**Cognitive and Adaptive Ability**

Intellectual disability is an associated characteristic of RTS. However, estimates made regarding the degree of intellectual disability have varied across studies. An early study
of those with the diagnosis who were institutionalised suggested an average IQ of 36 with a range of 15-59 (Padfield, Partington & Simpson, 1968). However, more recently an IQ estimate of 51 with a range of 30 to 79 in those who are not institutionalised has been suggested (Stevens et al. 1990). It is thought that most individuals lie within the mild to moderate range.

At present, a limited number of studies have documented cognitive or adaptive development in this syndrome. One questionnaire study by Stevens et al. (1990a) involving 50 individuals with RTS outlined difficulties with speech and reading skills. Speech difficulties were found in 90% of individuals and included problems such as speech delay and articulation difficulties. Reading ability was documented in 28 of the individuals and 67% could read. However, in all but three of these individuals reading was at an age equivalent level of only 7 years or younger. A later description of the syndrome by Baxter and Beer in 1992 made the suggestion that “speech is one of the slowest developmental areas for the child with this syndrome” (Baxter & Beer, 1992 p.453) The authors also made the suggestion that receptive language may be superior to expressive language in the syndrome and highlighted the possibility that some individuals may not develop speech.

A number of studies have demonstrated a short attention span in individuals with RTS. Stevens et al (1990a) conducted a questionnaire study and showed that ‘poor concentration’ was one of the most frequently reported problems, occurring in 76% of the individuals. Similarly, a survey conducted by Hennekam et al. (1992) using the Child Behaviour Checklist (CBCL) showed that 76% of individuals ‘can’t concentrate’ and was one of the most frequently reported problems. Interestingly, problems with attention measured by the CBCL have recently been replicated in a questionnaire study by Galéra et al. (2009). Individuals with RTS were scored significantly higher on the item ‘can’t concentrate/ pay attention for long’ than a control group matched for age, gender and developmental level. Such findings warrant consideration given the possible impact on educational and behavioural interventions.
Descriptions outlining the level of self help skills possessed by individuals with RTS are limited. However, Baxter and Beer (1992) mention that individuals will require assistance with their skills but “can become self sufficient in most self help areas, e.g. feeding, dressing, toileting etc” (Baxter & Beer, 1992 p.454) It may however, be important to note that self help ability may be affected by the tendency for individuals with RTS to experience motor difficulties. Goots and Liemohn (1977) assessed three children with RTS and described them as having more difficulties in planning motor acts and executing locomotor and oculomotor acts compared to individuals with non specific intellectual disability. Similarly, studies using the CBCL found individuals with RTS were frequently reported as ‘poorly coordinated’ and ‘clumsy’ (Galera et al 2009; Hennekam et al 1992)

Although research outlining the cognitive ability of RTS is limited, research has begun to make links between the molecular abnormalities and cognitive dysfunction found in RTS. The CREB binding protein implicated in RTS has been shown to underlie long term memory formation (Bourtchuladze et al. 1994; Yin et al, 1994; Bartsch et al. 1995) and consequently it has been suggested that cognitive deficits may occur as a result of impaired long term memory formation (D’Arcangelo & Curran, 1995; Weeber & Sweatt, 2002).

**Social Behaviour**

One of the most frequently documented characteristics in RTS is the ability to initiate and maintain social contact despite cognitive delay (Hennekam, 2006). Reports have described repeatedly those with RTS as “happy”, “loving”, “friendly” individuals who “know no strangers” and “love adult attention” (Baxter & Beer, 1992; Hennekam, 2006; Padfield, et al. 1968; Rubinstein & Taybi, 1963; Stevens et al. 1990a). Importantly, in one follow up study of eight individuals with RTS it was documented that “all individuals had social behaviour that allowed them to live in small group homes or their parents’ homes” (Partington, 1990 p.67).
More recently it has been suggested that the social communication and social competency skills shown in RTS are higher than those with other causes of intellectual disability (Hennekam et al 1992). Findings from comparison studies appear to support this assertion. Gotts and Liemohn (1977) compared three children with RTS to others with nonspecific intellectual disability and found that children with RTS were friendlier and more readily accepted social contacts. Similarly, a recent questionnaire study found that individuals with RTS scored significantly lower on a scale assessing ‘reduced contact or social interest’ than a matched control group. Findings indicated better social contact and social interest along several items including quality of eye contact, acceptance of physical contact, initiating play with other children, and looking up when spoken to (Galéra et al, 2009).

**Repetitive Behaviour**

Reports have indicated that individuals with RTS often show stereotyped movements such as spinning, rocking, and hand flapping. It has also been reported that approximately three quarters of children with RTS show behaviours such as insistence on sameness and adherence to routine. (Hennekam et al, 1992; Stevens et al, 1990a). Furthermore, in a recent comparison study using a matched control group, it was reported that individuals with RTS displayed significantly higher levels of repetitive behaviours. More specifically, individuals with RTS were scored higher on questionnaire items assessing ‘flaps arms/hands when excited’, ‘makes odd/fast movements with fingers/hands’ and ‘extremely pleased by certain movements/keeps doing them’ (Galéra et al, 2009).

In addition to the social behaviour and repetitive behaviours noted as part of the syndrome other behaviours have also been documented. Studies have highlighted stubbornness, impulsivity, hyperactivity, and sleeping difficulties (Gotts & Liemohn, 1977; Hennekam et al, 1992, Rubinstein & Taybi, 1963; Stevens, 2007; Stevens et al, 1990a). Other findings include a tendency for individuals to be “more emotional”, excitable and show a dislike for loud noises. (Gotts & Liemohn, 1977; Stevens et al, 1990).
Although the majority of descriptions describe children as generally happy and friendly, it has been suggested that individuals with RTS may experience behaviour change with age. Sudden mood changes, temper tantrums, uncertain behaviours and aggression have been identified in individuals during early adulthood (Hennekam, 2006). Case studies of older individuals appear to support this assertion. Verhoeven, Kuijpers, Wingbermühle, Egger & Tuinier (2008) described the case of a male aged 35 who was referred due to lowered mood, temper tantrums, anxieties and worrying. Similarly, Hellings, Hossain, Martin & Baratang (2002) described a 39 year old female who presented with mood lability and aggressive outbursts.

**Conclusions**

Rubinstein Tabyi Syndrome (RTS) is characterised by a distinct profile of physical, cognitive and behavioural features. Physical difficulties include failure to thrive in infancy, heightened risk of obesity in adolescence, heightened risk of cancer, respiratory infections, renal abnormalities and constipation. Furthermore, motor difficulties in this syndrome may impact on individuals’ self help abilities; however, with the right support and training individuals with RTS usually become sufficient in most self help areas.

In terms of cognitive ability, individuals with RTS generally have a mild to moderate intellectual disability, and are likely to have slower development of speech relative to other abilities. Short attention span, impulsivity and hyperactivity are likely to impact on an individual’s ability to perform successfully both inside and outside of educational settings, and this should be taken into account when planning educational and behavioural strategies. Long term memory may also be impaired in individuals with RTS so the use of strategies to help overcome memory difficulties (e.g. visual timetables, repeated exposure to information) may be essential in this syndrome.

A behavioural characteristic that is common in RTS is that individuals are more likely to want to engage in social communication than those with other syndromes. One danger is
that this desire for social contact coupled with intellectual disability may leave an individual vulnerable to social exploitation. It may be important to monitor the types of social interaction that an individual with RTS engages in, especially in the case of those individuals who are older and more independent. Individuals with RTS are also likely to engage in a range of repetitive behaviours and are likely to prefer predictable routines. Parents and clinicians should be aware that changes with age are reported in RTS such as increased mood swings, temper tantrums and aggressive outbursts and prepare for these changes. Future research should focus on why these changes with age occur.
References


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