

Facial expression of affect in children with Cornelia de Lange syndrome

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Abstract

Background. Individuals with Cornelia de Lange syndrome (CdLS) have been reported to show comparatively high levels of flat and negative affect but there have been no empirical evaluations. In this study we use an objective measure of facial expression to compare affect in CdLS with that seen in Cri du Chat syndrome and individuals with a mixed aetiology of intellectual disabilities.

Method. Observations of three groups of fourteen children with CdLS, Cri du Chat syndrome and mixed aetiology of intellectual disability were undertaken when a one-to-one interaction was ongoing.

Results. There was no significant difference between the groups in the duration of positive, negative or flat affect. However, the CdLS group displayed a significantly lower ratio of positive to negative affect than children in the other groups.

Discussion. This difference partially confirms anecdotal observations and could be due to the expression of pain caused by health problems associated with CdLS or neurological expression of the CdLS gene in facial muscles related to expression of positive affect. However, further research is needed to directly test these possible associations.

Introduction

Cornelia de Lange syndrome (CdLS) has an estimated prevalence of 1 in 50,000 live births (Beck, 1976; Beck & Fenger, 1985). To date, mutations in three genes have been found to cause CdLS: *NIPBL*, *SMC1A* and *SMC3*. Mutations in *NIPBL* account for approximately 20 to 50% of individuals diagnosed with CdLS, whilst mutations in *SMC1A* and *SMC3* account for approximately 5% of this population (Deardorff et al., 2007; Krantz et al., 2004; Tonkin, Wang, Lisgo, Bamshad & Strachan, 2004). Individuals with *NIPBL* mutations show large variability in presentation (both mild and classic forms) but a larger proportion of these individuals appear to have the classic form of the syndrome (Bhuiyan et al., 2006; Gillis et al., 2004). In contrast, mutations in *SMC1A* and *SMC3* have currently been found to only result in the mild phenotype of CdLS (Deardorff et al., 2007).

Individuals with CdLS typically have a low birth weight, small stature, upper limb abnormalities and hirsutism, although those with the mild phenotype seem less affected by these problems (Deardorff et al., 2007; Ireland, Donnai & Burn, 1993; Jackson, Kline, Barr & Koch, 1993; Kline et al., 2007; Selicorni et al., 1993). Distinctive facial features, including: synophrys; long, thick eye lashes; a long and prominent philtrum; a thin upper lip; and a downturned mouth appear characteristic of most individuals with the syndrome (Ireland et al., 1993; Jackson et al., 1993; Kline et al., 2007). Degree of intellectual disability is variable in CdLS but most show a severe or profound intellectual disability (30.43% severe level of intellectual disability; 45.6% profound level of intellectual disability) with notably poor expressive communication, primarily evidenced by limited or absent speech (Berney, Ireland & Burn, 1999; Goodban, 1993; Oliver et al., 2003; Sarimski, 1997). The degree of intellectual disability and level of communication skills seem dependent on the phenotype; those with the mild phenotype generally have a less severe degree of intellectual disability and appear more likely to acquire speech (Bhuiyan et al., 2006; Deardorff et al., 2007). CdLS is associated with many health problems. Some of the most commonly occurring problems are: hearing and eye abnormalities; and cardiac, genito-urinary and gastro-intestinal disorders (Jackson et al., 1993; Luzzani, Macchini, Valade, Milani & Selicorni, 2003).

A notable lack of facial expression of affect has been reported in CdLS. Johnson, Ekman, Friesen, Nyhan & Shear (1976) conducted a study to assess interactions between children with CdLS and a familiar adult or stranger. Participants were observed as showing a “lack of facial expression” with little movement in the upper areas of their faces. Additionally, participants were described as “nonsocial”, withdrawing from physical contact with either familiar adults or strangers. These observations together, have led to speculations of an increased prevalence of autism in CdLS. A study which used a postal survey to investigate the presence of an ‘autistic-like syndrome’ in 49 individuals with CdLS found that autism was “pronounced” in 37% and “intermediate” in 16% of participants (Berney et al., 1999). Recently, it was found that 61.8% of a group of individuals with CdLS assessed for autistic spectrum disorder using the Autism Diagnostic Observation Schedule (ADOS), scored above the cut-off for autism. This indicates there may be a high prevalence of autistic spectrum disorder associated with CdLS (Moss, Oliver, Jephcott, Berg, Kaur & Cornish, 2006).

Since Kanner’s (1943) early description of people with autism showing a deficit in “affective contact”, some research has been conducted into the expression of affect in this population. Several studies have shown that children with autism display less positive affect and more flat affect in social interactions when compared to matched individuals with intellectual disabilities (Bieberich & Morgan, 1998; Joseph & Tager-Flusberg, 1997; Yirmiya, Kasari, Sigman & Mundy, 1989). In contrast to these findings, some researchers have found that children with autism do not actually show an overall difference in the amount of positive affect displayed in social interactions when compared to typically developing children and children with intellectual disabilities. Rather, children with autism are less likely to show positive affect in communicative contexts, such as, joint attention situations and they are less likely to use positive affect in combination with other behaviours (e.g., eye contact) in social interactions (e.g., Dawson, Hill, Spencer, Galpert & Watson, 1990; Kasari, Sigman, Mundy & Yirmiya, 1990). The inconsistent findings on expression of affect in children with autism are likely to be due to differing methodologies between studies. However, overall the results suggest that children with autism are less efficient at using expression of affect in social interactions either because they use less positive affect in an interaction or they use positive affect less effectively in conjunction with other communicative behaviours. The possibility of a raised prevalence of autism in

CdLS in combination with observations of lack of expression of affect in the syndrome is a good reason to empirically examine expression of affect in this group.

A second reason for investigating expression of affect in children with CdLS is the raised prevalence of painful gastro-oesophageal reflux (GER). A study of 310 individuals with CdLS found that 80 (25.8%) participants had documented GER. They also noted that GER often caused behavioural change after meals-times, such as, back arching, hyperactive behaviour and other manifestations of distress (Jackson et al., 1993). In addition, Luzzani et al. (2003) examined GER in 43 individuals with CdLS and found 65% evidencing various degrees of oesophagitis. The most frequently presenting symptoms when GER occurred were hyperactivity (85%), vomiting (53%) and nocturnal agitation (50%). Improvement of these signs was noted after treatment, which suggests a relationship between GER and presenting symptoms. In a study of health problems in individuals with genetic syndromes, an association was found between health problems and low affect (Berg, Arron, Burbidge, Moss & Oliver, 2007). Individuals with a health problem were approximately three times more likely to experience low affect than those with no health problems.

This is an important association in people who may not be able to report on their internal state. The assessment of pain in these circumstances relies on other indicators and third party observations (Stallard, Williams, Lenton, & Velleman, 2001). Facial expression has been acknowledged as an important indicator of pain (Stallard et al., 2002). For example, the most important indicator of pain in a tool developed to identify pain in cognitively and communicatively impaired children with life threatening illness was “screwed up or distressed looking face” (Stallard et al., 2002). This marker on its own correctly classified 87% of pain / non-pain episodes. Thus, facial expression of low affect is important to evaluate in CdLS given the degree of intellectual disability associated with the syndrome and documented poor expressive communication. Furthermore, there is some evidence which suggests that individuals with CdLS may show high levels of negative affect. Sarimski (1997) found that 12% of 27 individuals with CdLS were sad and 46.2% experienced very frequent mood changes. This facial expression of negative affect could be indicative of health problems.

In this study we assess facial expression of affect displayed by children with CdLS in a relatively controlled natural setting, whilst engaging in a one-to-one interaction with adults. The study will examine whether facial expression of affect differs in children with CdLS in comparison to children with Cri du Chat syndrome (CDC) who have a comparable degree of intellectual disability (Sarimski, 2002) and a heterogeneous comparison group of children with intellectual disabilities (HID). In order to effectively compare the percentage of time participants displayed positive and negative affect, a ratio of positive to negative affect will be used in the analysis. The aim of the study is to use objective measures of facial expression of affect to examine the differences in positive, negative and flat affect displayed across the three groups matched for age, gender, mobility and level of intellectual disability.

Method

Participants

Fourteen individuals diagnosed with CdLS, fourteen individuals diagnosed with CDC and fourteen individuals with a mixed aetiology of intellectual disabilities participated in the current study. All participants were recruited from three previous studies in which natural observations of participants had been recorded (Arron, 2003; Cornish & Bramble, 2002; Sloneem, 2003). The sample size chosen for the current study was based on the ability to match participants from all three groups and based on the number of videos that could be coded given the time constraints of the study. The inclusion criteria for all participants in the present study consisted of: availability of 20 minutes of video footage of one-to-one interaction with an adult in a classroom setting, age range of two to sixteen years old and confirmed diagnosis of CdLS / CDC (depending on group allocation).

The CdLS group was randomly selected and consisted of seven females and seven males, with an age range of 2-15 years (mean age of 6 years). The individuals with CDC were matched to participants in the CdLS group according to age, gender, mobility and level of intellectual disability. The Receptive and Expressive subdomain scores from the Vineland Adaptive Behavior Scale (VABS; Sparrow, Balla & Cicchetti, 1984) were used to compare the groups on degree of intellectual disability. The VABS scores were not available for one of the participants in this group, so

matching for this participant was based on age, gender, mobility and their Self help skills score from the Wessex Scale (Kuschlick, Blunden & Cox, 1973). The CDC group consisted of seven females and seven males with an age range of 4-15 years (mean age of 7.2 years).

A heterogeneous comparison group of children with intellectual disabilities (HID) was also matched to the other groups according to age, gender, mobility and level of intellectual disability. Where possible individuals were matched using the Daily Living Skills domain age equivalence score from the VABS (Sparrow et al., 1984). However, most individuals were matched using the Self help skills score from the Wessex Scale (Kuschlick et al., 1973). The HID group consisted of ten participants with no specific diagnosis and four individuals with identifiable syndromes, including Reye syndrome (n=1) and Down syndrome (n=3) (six females, eight males; age range 4-15 years (mean age of 7.5 years) (See Table 1.).

+++++ Table 1 here +++++

Procedure

In the previous studies, each child was videotaped for between one and a half and four and a half hours during a 'typical day' in their classroom (Arron, 2003; Cornish & Bramble, 2002; Sloneem, 2003). We edited the videos to obtain the first 20 minutes of one-to-one interaction with an adult. This was defined as, the adult being within two metres of the participant. The settings included registration, play time, reading and academic sessions.

Observational coding, response definitions and inter observer reliability

Videotapes were coded using partial interval time sampling with 10s time intervals. Two codes were used to assess facial expression of affect. *Positive affect* was defined as laughing and smiling, as evidenced by spreading of lips, up-turning of corners of mouth, raising of cheeks and horizontal creases lateral to eyes. *Negative affect* was defined as crying and grimacing, as evidenced by down-turning of corners of mouth, lowering of cheeks and two vertical creases on forehead.

Two observers each coded half of the videotapes independently and then coded the first four minutes of the videotapes that had been coded by the other observer. Hence, the first four minutes of each 20 minute tape were coded by both observers. Kappa coefficients, based on ten second intervals, for positive and negative affect were .77 and .90 respectively. This indicates a relatively high level of inter observer reliability.

Data Analysis

The percentage of intervals that positive and negative affect was observed in the 20 minute period was calculated for participants in each group. The percentage of intervals in which participants displayed neither positive nor negative affect was deemed to be the percentage of intervals in which participants displayed flat affect. To examine the relative differences in positive and negative affect between the groups, the ratio of the percentage of intervals in which participants displayed positive affect to negative affect was examined. However, as most participants in the CDC and HID groups did not display negative affect, this ratio was in calculable as zero in a ratio precludes calculation. Therefore, the ratio of the percentage of intervals that children *did not* display negative affect to *did not* display positive affect was calculated and used in the analysis. As the ratio of the percentage of intervals that children *did not* display negative affect to *did not* display positive affect is indicative of the ratio of the percentage of intervals that participants displayed positive affect to negative affect, the latter term will be used.

Results

Descriptive Statistics

To ensure that the three groups were matched on age, gender and level of intellectual disability, comparisons were conducted. A one-way ANOVA revealed that there was no significant difference in age between the three groups ($F(2, 39) = .68, p = .51$) and a chi-square test indicated no significant difference in gender between the groups ($\chi^2(2) = .19, p = .91$). Results of a one-way ANOVA (Expressive and Receptive communication age equivalent in months taken from the VABS) indicated no significant difference between the three groups on VABS Receptive communication age equivalent in months ($F(2, 38) = .35, p = .71$) or VABS Expressive communication age equivalent in months ($F(2, 38) = .34, p = .72$). Thus, the groups

are comparable in terms of age, gender and VABS Expressive and Receptive communication age equivalent in months.

Analysis of Affect

In order to assess differences in facial expression of affect displayed by the group of children with CdLS in comparison to the children with CDC and HID, the median percentage of intervals that participants displayed positive, negative and flat affect, were compared.

As the data were not normally distributed, Kruskal-Wallis one-way ANOVAs were used to assess differences in the percentage of intervals that participants displayed positive, negative and flat affect. The median percentage of intervals that participants with CdLS showed positive affect (median = 2.59%, mean = 3.55%) was less than the two comparison groups (CDC: median = 6.3%, mean = 7.32%; HID: median = 5.16%, mean = 6.92%). A Kruskal-Wallis one-way ANOVA revealed that there was no significant difference for the percentage of intervals that positive affect was displayed, between the groups ($\chi^2(2) = 4.48$, $p = .11$). In addition, there was no significant difference between the three groups in the median percentage of intervals that participants showed negative affect, although the level of statistical significance was marginal (CdLS: median = 0%, mean = 1.02%; CDC: median = 0%, mean = .21%; HID: median = 0%, mean = .03%; ($\chi^2(2) = 5.89$, $p = .05$). Finally, a Kruskal-Wallis one-way ANOVA was performed for the percentage of intervals that participants displayed flat affect and again the results indicated that there was no significant difference between the groups ($\chi^2(2) = 1.88$, $p = .39$). In summary, there was no significant difference between the three groups for the percentage of intervals that participants displayed positive, negative and flat affect.

The median ratio of the percentage of intervals that participants displayed positive affect to negative affect, in each group can be seen in Figure 1. These data show that the median ratio of the percentage of intervals in which participants displayed positive affect to negative affect, was smaller for children with CdLS (median = 1, mean = 1.03) than the two comparison groups (CDC: median = 1.07, mean = 1.08; HID: median = 1.05, mean = 1.08). A Kruskal-Wallis one-way ANOVA indicated a significant difference in the ratio of the percentage of intervals that children showed

positive affect to negative affect, between the three groups ($\chi^2 (2) = 6.25, p = .04$). Post hoc analysis of differences using the Mann-Whitney test indicated a significant difference between the CdLS and CDC groups ($U = 51.5, p = .03$), a significant difference between the CdLS and HID groups ($U = 51, p = .03$), but no significant difference between the CDC and HID groups ($U = 94, p = .85$). Thus the ratio of the percentage of intervals in which children displayed positive affect to negative affect was significantly lower for the children in the CdLS group than the children in the CDC group and the HID group.

+++++++ insert figure 1 here ++++++

Discussion

This study is the first to measure facial expression of positive, negative and flat affect in children with CdLS using reliable observational measures and employing appropriate control groups. Although there were no significant differences between the three groups for flat, positive and negative affect, the latter difference approached significance and the children in the CdLS group displayed a significantly lower ratio of positive to negative affect than participants in both the CDC group and the HID group.

These observations may be indicative of the physical health problems reported in CdLS, such as GER. Although no study to date has assessed affect as an indicator of pain for GER in children with CdLS, ‘facial expression’ has been acknowledged as a strong individual predictor of pain in individuals with severe cognitive impairment (Stallard et al., 2002). One possible explanation for the finding is that the expression of pain due to GER caused participants in the CdLS group to display a significantly lower ratio of positive to negative affect. Berg et al.’s (2007) finding that individuals with health problems are approximately three times as likely to experience low affect, further supports this explanation, as it indicates a strong association between affect and health problems. Future research is needed to establish whether children with CdLS show higher levels of negative affect if assessed when medical conditions are present. For example, individuals with CdLS who have GER need to be assessed around meal-times because this is known to be painful for people with GER.

The role of genetics in CdLS may also help to account for the significant difference found between the groups in the ratio of positive to negative affect shown by participants. The three genes currently identified to cause CdLS account for up to 55% of people with the syndrome and further research is being undertaken to establish which other genes account for the syndrome (Deardorff et al., 2007; Krantz et al., 2004; Tonkin et al., 2004). Once further research has been conducted to fully establish the role of genetics in CdLS, we will be able to determine whether there is an abnormal expression of genes in the craniofacial region of individuals with the syndrome, particularly given that the facial characteristics are so marked in individuals with the classic form of the syndrome. Therefore, through further research we will be able to establish whether the genetic disorder that causes CdLS affects the development of the facial muscles and causes a reduction in some facial expressions, such as smiling and thus accounts for the current findings.

The results showed no significant differences between the three groups in the amount of positive and negative affect displayed by participants. A similar pattern of affect has also been found in some studies of children with autism. Research has suggested that children with autism show no significant difference in the amount of positive and negative affect they express in social interactions when compared to typically developing children and children with intellectual disabilities of a similar ability (Dawson et al., 1990; Kasari et al., 1990). Instead, children with autism are less likely to combine positive affect with other communicative behaviours in social interactions and they are less likely to use positive affect in joint attention situations than the matched comparison groups (Dawson et al., 1990; Kasari et al., 1990). Other communicative behaviours were not coded as part of the study but given the high prevalence of autistic spectrum disorder associated with CdLS, it would be of interest to examine whether children with CdLS show a similar use of positive expression of affect to children with autism in social interactions (Moss et al., 2006).

The results also indicate no significant difference in the expression of flat affect displayed by participants across the three groups. This finding appears not to support the observations made by Johnson et al. (1976), which described children with CdLS as showing a “lack of facial expression” and appearing “inexpressive”. On the other

hand, although the duration of flat affect did not differ significantly between the groups, the context in which individuals in each group showed flat affect may have varied. For example, it may have been that children with CdLS were flat in the expression of affect when the adult interacting with them expected a positive response, whereas the children in the comparison groups may have used their expressions of affect more appropriately in each situation. A more detailed study examining the expression of flat affect in relation to environmental cues, such as, the facial expression of the other person in the interaction, is needed to determine whether there is empirical support for Johnson et al.'s observations (1976).

Overall, the levels of positive and negative affect shown by participants in all three groups were relatively low and in particular almost no negative affect was shown by all participants in each group. This then raises the question about what other communicative behaviours were displayed by participants during the interactions. As mentioned previously, research indicates that children with autism are less effective at using communicative behaviours during social interactions (Dawson et al., 1990; Kasari et al., 1990). A future study is needed which encompasses the assessment of autism in conjunction with the examination of a range of behaviours known to be involved in communication. We could then determine whether those individuals with CdLS who score higher on a measure of autism, show a similar pattern of behaviour to children with autism in social interactions or whether a specific profile of communication is seen across individuals with CdLS irrespective of the presence of autistic spectrum disorder.

There are some limitations to this study, which may effect the interpretation of the findings. First, in the one-to-one interaction, it was not possible to control the nature of the tasks which the children took part in. Certain activities may have provided the setting for an increase in positive affect in comparison to other tasks. However, as participants and tape samples were randomly selected, the nature of the tasks should have been randomly distributed between the groups. The limited time sample may have softened some effects. Symptoms that co-occur with GER tend to present after meal-times because GER manifests after food consumption (Jackson et al., 1993). This may explain why the children in the CdLS group in the present study did not display significantly higher levels of negative affect. Additionally, the health problems of the participants were unknown, so an assessment of how affect related to

participants' health problems could not be conducted. Therefore, it was not possible to confirm whether the findings were due to the health problems from which children with CdLS suffer.

In addition, a note of caution must be applied to the interpretation of levels of flat affect across all groups. Operational definitions were developed for the expression of positive and negative affect and these were coded for each participant. The expression of flat affect was then assumed to be the time when participants were displaying neither positive nor negative affect. However, it may have been that participants were actually showing 'blends' of facial expressions, rather than flat affect during the time when neither positive or negative affect was shown. Yirmiya et al. (1989) used a detailed coding system to examine facial expressions in children with autism and found that they displayed significantly more negative and incongruous 'blends' of facial expressions than two matched comparison groups. Again, considering there is an association between CdLS and autism, a more fine-grained coding system of facial expression would be appropriate for future research to determine whether individuals with CdLS show 'blends' of expressions in social interactions.

Despite these limitations, results indicate a lower ratio of positive to negative affect is evident in children diagnosed with Cornelia de Lange syndrome. This could be due to the expression of pain caused by gastro-oesophageal reflux or may be indicative of neurological dysfunction in children with CdLS involving the movement of facial muscles, which could cause a reduction in behaviours, such as smiling. Alternatively, the expression of affect may form part of a pattern of communication shown by individuals with CdLS in social interactions. Further research will enable us to explore these hypotheses further and help to account for the findings of the current study.

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Table I. CdLS, CDC and HID Group; Age (Mean, *SD* and Range), Gender and Mean (*SD*) Vineland Adaptive Behavior Scale (VABS) Scores for the Receptive and Expressive Domain Age Equivalent in Months.

	CdLS	CDC	HID
Mean Age (Years)	6.00	7.21	7.50
<i>SD</i>	(3.90)	(3.51)	(3.44)
Range	(2-15)	(4-15)	(4-15)
% Male	50	50	57.1
Mean VABS receptive domain age equivalent (months)	25.7	20.8*	26.1
<i>SD</i>	(24.2)	(8.9)*	(17.8)
Mean VABS-expressive domain age equivalent (months)	16.9	18.8*	20.8
<i>SD</i>	(11.2)	(11.2)*	(14.5)

* One participant's data missing (n = 13).

Figure 1. Median ratio of the percentage of intervals participants displayed positive affect to negative affect (error bars show inter-quartile range).

