

Behaviour in Cornelia de Lange syndrome: a systematic review

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ABBREVIATIONS

ASD	Autism spectrum disorder
CdLS	Cornelia de Lange syndrome
SIB	Self-injurious behaviour
VABS	Vineland Adaptive Behavior Scales

AIM Careful study and accurate description of behaviour are important to understand developmental challenges for individuals with Cornelia de Lange syndrome (CdLS). Here we present a systematic review of current understanding of behaviour in CdLS.

METHOD A systematic search was performed for articles published between January 1946 and December 2015 evaluating autism, self-injury, and/or cognition in CdLS. After study-selection, 43 papers were included. The Cochrane quality criteria were adjusted to assign quality scores to the included studies.

RESULTS Participants were mostly categorized in the severe/profound developmental level. Methodology and quality were very heterogeneous, as well as reporting occurrence of autism. Self-injurious behaviour was reported in 15 papers. Physical conditions were reported in 21 studies, mostly related to hearing and vision. Only nine studies mentioned details about medication.

INTERPRETATION Comparison of presented results was hindered by heterogeneous assessment methods. Improving our understanding of behavioural characteristics in CdLS requires more uniform methodology. We propose a criterion standard of instruments that can ideally be used in assessment of behaviour and development. This will improve understanding of behaviour in the context of developmental level and daily functioning.

Cornelia de Lange syndrome (CdLS) is a genetic disorder characterized by distinctive facial features, limb abnormalities, and intellectual disability. The syndrome is mainly caused by mutations in the genes *NIPBL*, *SMC3*, and *SMCIA*.^{1–3} Reported levels of intellectual functioning range from normal/borderline to profoundly disabled.^{4,5} The behaviour seen in CdLS includes autism characteristics, self-injurious behaviour (SIB), aggression and expressive-receptive language discrepancy.^{6–8} Anxiety (particularly social anxiety), aggression, and SIB are examples of behaviour that disrupt daily functioning.⁹

In the past decades, several studies have been performed to identify the behavioural phenotype in CdLS.^{7,10–13} However, to our knowledge no systematic review of published studies on behaviour in CdLS has previously been undertaken. Careful study and accurate description of behaviour is important to understand developmental challenges for individuals with CdLS. Collating this information will improve future research and will eventually inform treatment. Here we present a systematic review of current understanding of behaviour in CdLS. We highlight five areas of interest, namely developmental level, autism

spectrum disorder (ASD), SIB, physical conditions, and medication use. Methodology and quality of publications will be systematically evaluated to enable insight in strengths and weaknesses of previous behavioural research in CdLS, so as to improve future research on behavioural phenotypes in CdLS and other rare genetic disorders.

The main aim of this study is to identify what we already know about the behavioural phenotype in CdLS and which questions still remain.

METHOD

Literature search

A systematic search for articles published between January 1946 and December 2015 evaluating autism, self-injury, and/or cognition in CdLS was performed in two steps. First, index terms and free-text words were identified from an initial set of papers retrieved by random search (Table SI, online supporting information). These terms were used to systematically search the online literature databases PsychINFO, EMBASE, and Ovid MEDLINE for relevant papers. Searches were performed by combining terms for phenotype AND/OR behaviour AND/OR autism

AND/OR cognition AND/OR self-injurious behaviour with search terms for CdLS (including Brachmann-de Lange syndrome). Titles and abstracts were checked for eligibility. In the second step, references of the included papers were checked for additional relevant papers (snowballing).

Study selection and data extraction were performed by two reviewers (PAM and SP), who scored all identified papers independently from each other. Consensus was sought in case of discrepancies by consulting a third reviewer (IDCvB). Papers published in English, German, French, Spanish, or Dutch were eligible for review if they presented original research; if participants had a confirmed diagnosis of CdLS (molecularly confirmed or clinically validated by an experienced clinician); if series of at least three participants were described; and if behaviour was described. When validation of diagnosis was not defined and authors could not be reached for a definitive answer, papers were excluded. Three studies that reported confirmed diagnosis based on parent reports were included.^{14–16}

Risk of bias was reduced by removing duplicates. We checked all studies for method of recruitment (Table SII and Appendix S1, online supporting information).

Data extraction

Two reviewers (PAM and SP) systematically extracted data through a standardized data-extraction form. Study design, population, and behavioural characteristics were extracted. The appraisal form was based on subscales from questionnaires such as the Problem Behavior Inventory-01¹⁷ and Social Communication Questionnaire,¹⁸ direct assessment subscales from the Autism Diagnostic Observation Schedule¹⁹ and an adapted version of the Cochrane data collection checklist.²⁰ The following variables were extracted: country, study population, acquisition, genotype, assessment method, study design, number of participants, age, outcome measure, quality assessment, used instruments, physical condition, medication, developmental level, ASD, SIB, and other behaviour.

The Cochrane quality criteria were adjusted to suit the included studies and their methodology. We adapted the Cochrane data collection checklist using the following criteria: baseline measurement included, assessment/intervention is independent of other changes, data were obtained through validated and standardized instruments, data collection was unlikely to have been affected by assessment/intervention, blinded assessment of primary outcome(s), completeness of dataset and reliable primary outcome measure(s). Criteria were scored as follows: done, not clear, not done, and not applicable.

These criteria were applied to the behavioural outcome measures, even when these were not the main outcome measures of the study. Other outcome measures were not scored in accordance with the aim of this review. Papers could receive a maximum score of seven out of seven only when study design included a baseline measurement. When study design did not allow a baseline measurement, studies

What this paper adds

- Improving understanding of behaviour in Cornelia de Lange syndrome requires more uniform methods and quality.
- Combining a survey approach with direct in-person assessments is necessary.
- A criterion standard of assessment methods is presented.

could receive a maximum score from six out of six (Appendix S1, online supporting information).

RESULTS

We identified 551 papers and selected 43 eligible papers to include in the review (Fig. S1).

Table SII presents a summary of key study characteristics (more detailed information in Appendix S1). Notably, most participants were recruited through National Foundations of Parent Support (74%). Eight papers (19%) used only questionnaires for data collection, 34 papers (79%) used two or more methods (e.g. questionnaire, interview, and/or observation) of data collection, and 14 papers used a direct assessment tool (33%). Twenty studies used one or more comparison group(s) (47%). Mutation analyses were performed in six studies (14%). Nine papers mentioned medication use by participants (21%).^{8,11,12,21–26} Limited specifics were provided regarding medication use, information ranged from ‘numerous medications’ and ‘antipsychotic medication’ to medication used for ‘hyperactivity, sleep problems, or aggressiveness’. Data on effectiveness of medication were presented in three studies only, ranging from ‘without success’ and ‘minimal to variably positive’ to ‘33% useful’.^{11,21,24}

Appendix S2 contains information on key outcomes on behaviour and development. Studies that did not use standardized assessments ($n=7$) were excluded from further behavioural analysis. Thirty-six papers were included. Thirty-one of these studies reported on developmental level (86%), 19 studies reported on ASD (53%), 15 presented information about SIB (42%), 21 studies show details on physical conditions (58%), and nine studies presented data on use of medication (25%). From Appendix S2 it becomes clear that assessment tools for studying behavioural characteristics vary widely depending on the focus of the study. For example, methodology of describing ASD phenomenology differs strongly. Some studies give only mean scores and/or cut-off scores from used assessment tools,^{3,27} other studies describe the observed behaviour in more detail.^{13,28}

Six studies reported the presence of mutations in one or more genes.^{3,5,29–32} Four of these studies stratified data by genetic cause for development and behaviour. Nakanishi et al.³ reported Autism Diagnostic Interview-Revised (ADI-R) and Vineland Adaptive Behavior Scales (VABS) results for patients with an *NIPBL* mutation ($n=22$) and ADI-R results for patients with an *SMC1A* mutation ($n=3$). The authors did not find significant differences in ADI-R scores between the two genotypes. Patients with an *NIPBL* mutation had a VABS Adaptive Behavior Composite score of 57. Pié et al. reported mild ($<2y$, $n=3$), moderate ($>2y$, $n=3$), and severe ($n=1$) developmental delay in patients with

an *NIPBL* mutation. One patient with an *SMC1A* mutation had a moderate delay.³¹ The study by Kline et al. reported results on intellectual disability in patients with an *NIPBL* mutation ($n=13$) and one patient with an *SMC1A* mutation. Eight patients with an *NIPBL* mutation had a severe intellectual disability and five had a mild intellectual disability. One patient with an *SMC1A* mutation also had a mild intellectual disability.³² Bhuiyan et al. described adaptive functioning of patients with an *NIPBL* mutation ($n=22$) using the VABS. Mildly/moderately impaired adaptive functioning was found in six patients and severely/profoundly impaired adaptive functioning in 16 patients. Autism was found in 15 patients according to the Diagnostic Interview for Social and Communication Disorders (no autism: $n=7$) and in 12 patients according to the Developmental Behavior Checklist (no autism: $n=10$).²⁹

Five areas of interest

To highlight results on the five areas of interest in this systematic review, we selected studies that scored four out of six or five out of seven quality criteria and present these in Table SIII (online supporting information). We report the most noteworthy results from these studies.

With regard to developmental level, as expected, most participants (33–74%) were categorized as profoundly/severely disabled. Three studies report developmental level in age equivalent scores according to the VABS.^{8,14,33}

In this selection of 14 studies, seven articles studied the presence of ASD. Presence of ASD was reported in different categories according to the specific assessment method used. For example, Oliver et al. report presence of ASD based on videotaped observations measured with the Childhood Autism Rating Scale and present results in categories ‘no autism’, ‘mild to moderate autism’, and ‘severe autism’, where Berney et al. report the presence of ASD as ‘pronounced’, ‘indeterminate’, and ‘absent’ according to the judgement of an experienced clinician based on the results from postal questionnaires.^{8,11} Results in these studies showed that ASD is scored in 27% to 82% of the participants.⁸

Eight out of 14 studies reported results regarding SIB. SIB is present in 25% to 62% of studied participants. One study used SIB as an inclusion criterion, so SIB was present in all participants.¹⁴ Five studies reported specific forms of SIB,^{11,14,23,29,34} two reported only on the presence of SIB,^{4,25} and one reported frequency of occurrence.⁵ Most reported specific forms of SIB are (self-)biting (5 out of 5 studies), head banging (3 out of 5 studies), and (skin) picking (2 out of 5 studies).

Physical conditions were reported in eight articles, with the most reported physical conditions being vision problems, hearing problems, and limb reduction. Hearing problems were reported in 7% to 80% of participants, and vision problems in 6% to 67%. Limb reduction was seen in 20% to 44% of participants. Other commonly mentioned symptoms were gastroesophageal problems, cleft palate, and limited mobility.

Medication is the last area of interest. Very few studies presented data on medication, with four studies reporting drug-groups used, including anti-psychotics, anti-epileptics, non-psychoactive medicines, and sleep medication. Only one study mentioned (parent/carer reported) efficacy in medication used for reducing SIB, ‘Few had tried medication and, of those who had, only 33% found it useful’.¹¹

DISCUSSION

In this systematic review we present data from 43 eligible studies which studied behaviour in CdLS. To our knowledge this is the first systematic review on behavioural characteristics in CdLS. It highlights five areas of interest, namely developmental level, ASD, SIB, physical conditions, and use of medication. This review also considered methodological properties. No firm conclusions on developmental and behavioural phenotype in CdLS can be drawn because of the heterogeneity of used assessments, variety in reported data, and methodological differences.

Developmental level

According to Table SIII, 31 studies presented data on developmental level. The results from the 14 selected studies show that, as expected, most participants (33–74%) were categorized as profoundly/severely disabled. Developmental level was mostly determined through the VABS. Direct in-person cognitive assessments were performed in only seven studies. Several instruments were used in direct in-person assessments, and description of data differed from individual IQ scores to International Classification of Diseases and related health problems (ICD-10) classifications. Description of results in specific task performances such as verbal tasks, performance tasks, memory, and processing was lacking in all studies. This would have been of interest, because for example Ajmone et al.³⁰ found that short, non-verbal tests such as the Leiter scale may be preferable (in their study population) to the Wechsler scales because the Leiter scale demands less of language, attention, and motor skills.

The VABS, an indirect assessment, was widely used. Assessments like the VABS offer an indirect indication of a person’s abilities in daily functioning. They provide insufficient information on individual limitations, possibilities to tackle these, and what implications this may have for social and learning environments.

Autism spectrum disorder

Assessment of ASD was undertaken in 19 studies, and was mostly based on parent/carer informed questionnaires or interviews. Results were reported in cut-off scores and sometimes highlighted some specific characteristics (e.g. repetitive behaviour, social withdrawal, and play). ASD was found in 27% to 82% of participants. Two studies performed direct in-person assessments with the Autism Diagnostic Observation Schedule, both offered more specific information on ASD-behaviour seen in CdLS (e.g.

significantly greater anxiety in CdLS group than the ASD group).¹³ When studying behaviour such as ASD in CdLS and other rare genetic syndromes, an important issue is the difficulty in differentiating between behaviour as part of ASD or as part of (severe) intellectual disability. As Bhuiyan et al.²⁹ pointed out, the number of ASD characteristics seen in CdLS increases when the level of adaptive behaviour decreases. It is important to evaluate ASD symptoms in individuals with intellectual disability carefully and accurately, as a diagnosis of ASD is based on behaviourally defined criteria. An individual with a (severe) intellectual disability may meet the diagnostic criteria for ASD, even though his abilities match his developmental age.

Self-injurious behaviour

Data on SIB were presented in 15 papers, which is relatively few because SIB is regularly seen in CdLS (SA Huisman, personal communication 2015).^{12,34} Most described forms of SIB were biting, (head-)banging, and (skin) picking. All studies mentioned also other forms of SIB. SIB entails tremendous distress to the individual, parents, and caregivers. Studying this behaviour is important to inform guidelines for interventions to reduce SIB. In general, in these studies' data were gathered through parent/carer informed questionnaires or interviews, with only four studies including observational data. As pointed out before, combining indirect with direct assessments is necessary to precisely map this behaviour within certain environments. Aspects influencing SIB are social context and social interaction, biological factors, somatic issues, level of intellectual disability, and communicative abilities.^{14,15,35} Efficacy of reinforcement-based treatment of SIB may be improved by use of a functional assessment.³⁶ Executing a functional assessment has the advantage of studying SIB in the context of an individual's daily life.

Physical conditions

When presenting data on level of development, ASD, SIB, or other behavioural characteristics, it is important to report possible physical constraints as they may interfere with a person's abilities. Data on physical conditions were reported in 21 studies only, mostly by means of the Wessex scale.³⁷ Eight out of 14 selected papers presented data on vision and hearing impairments and limb reduction. Visual and hearing impairments were observed in 6% to 67% and 7% to 80% of individuals respectively, and limb reduction in 20% to 44% of participants. It is well known that, in addition to intellectual disability, sensory impairments may cause limitations in communication which can lead to challenging behaviour.³⁸⁻⁴⁰ Physical discomfort (most reported were gastroesophageal problems and dental/mouth problems) is also a risk marker for challenging behaviour.⁴¹ Considering possible concurrent physical issues when assessing individuals remains of utmost importance to understand the implication of certain behaviours.

Medication

Remarkably, medication use was reported in nine studies only. Elucidation was mainly limited to type and indication (e.g. anti-epileptic, anti-psychotic, hyperactivity, and sleep problems). Little was mentioned on effect (e.g. 'no improvements' or 'useful'). No data on doses were provided, and hardly any additional information was provided on indication and efficacy. This lack of published data (group level) on pharmacological effects may hinder prescription of effective medication by healthcare professionals.

It is striking that sensory processing⁴² has hardly been studied in CdLS. Information is available on hearing and visual problems, but the impact of aberrant sensory processing in daily life in CdLS is unclear. Following the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5), sensory processing is an important domain to be looked for when ASD is being studied.⁴³ Impaired sensory processing can, next to hearing and visual problems, influence the way stimuli are processed and interpreted. Understanding the individual's sensory processing style may also be useful for adapting communication strategies in daily functioning.

An additional noteworthy finding is that only a few studies performed a genetic analysis. This is partly because 11 studies were conducted before specific causal gene mutations were identified in CdLS in 2004.^{1,2} Six studies found one or more gene mutations, of which four reported developmental and/or behavioural data stratified to genetic cause.^{3,29,31,32} Such limited data preclude definite conclusions. Future studies should not only perform genetic analysis, but also stratify physical and behavioural data by genetic cause(s). Different genotypes may entail different observable behavioural patterns and mapping these molecular subgroups carefully could support identification of concurrent patterns in clinical behaviour.

Methodological characteristics

Behavioural outcome measures were as diverse as assessment methods, in part because of several conceptual and practical considerations. Thirty-six papers used questionnaires (sometimes combined with other assessment methods) to gather data. Using a survey approach may improve feasibility of a study⁹ because it increases the accessibility of a population. However, the phenotype in CdLS is diverse; to cover the whole population, researchers should not restrict participation to national patient foundations and/or parent support groups, as this carries the risk of selection bias. Recruitment should also take place through professionals and healthcare institutions.

Because no suitable quality assessment method for behavioural studies was found fitting the goal of this review, we adapted relevant items of the data collection checklist from the Cochrane Effective Practice and Organisation of Care Review Group.²⁰ None of the included papers achieved a maximum score. Criteria most often unmet were inclusion of baseline measurement, blinded assessment of primary

Table I: Recommended assessment methods in (rare) syndromes

Outcome measure	Assessment/characteristics
Cognition	Bayley-III, ⁴⁵ Wechsler Nonverbal Scale of Ability ⁴⁶
Adaptive functioning	Vineland Adaptive Behavior Scales ⁴⁷
Autism spectrum disorder (characteristics)	Autism Diagnostic Observation Schedule, ¹⁹ Autism Diagnostic Interview-Revised, ⁴⁸ Social Communication Questionnaire ¹⁸
Sensory processing	Sensory Profile ⁴²
Self-injurious behaviour	Behavior Problems Inventory – 01, ¹⁷ direct assessment and/or observation, Challenging Behavior Interview ⁴⁹
Physical characteristics	Vision, hearing, mobility (e.g. Wessex scale ³⁷), physical evaluation
Medication	Label, indication, doses, effect
Context of daily life	Environment (e.g. developmental history, residence), support (e.g. speech therapy, paediatrician)

outcome(s), and reliable primary outcome measure(s). This is related to behaviour not being an objective outcome (such as laboratory test values, length or height), inter-rater reliability was often lower than 0.80 (kappa), and only a few studies used matched controls.^{8,28,44} Therefore, lower scores do not necessarily reflect the potential value of a study; rather, they may be considered an indication of the diverse nature of assessed studies and the broad inclusion criteria.

There is a clear need for more uniform assessment of behaviour in individuals with CdLS using appropriate, validated instruments. Direct in-person individual assessments as well as assessment of the developmental phase and cognition should become a routine part of studying behaviour in rare syndromes. Table I contains a proposal for more uniform assessment of behaviour in (rare) genetic syndromes using high-quality instruments.

Strengths and weaknesses

A strength of this study is that the extensive search method minimized selection bias and data were systematically extracted by two independent researchers by means of a standardized appraisal form. We not only systematically evaluated behaviour that was reported, but also evaluated the method and quality of the studies. This increases the usefulness of this review for future behavioural studies in other (rare) syndromes.

A possible weakness is that there was no suitable method available to evaluate the studies on their methodological quality. This was because of the heterogeneity of study designs and outcome measures. However, to provide insight into the quality of the papers, the commonly used

Cochrane quality criteria were adapted to evaluate the quality of the articles in the most objective way.

We aimed to reduce the risk of bias by removing duplicates. In addition, our aim was to identify current knowledge regarding behaviour and development of persons with CdLS rather than comparing and summarizing effectiveness of interventions, causing bias to be less of an issue. Three studies described different selections of outcome measures for the same participant population.^{8,25,34} Moreover, few researchers study behaviour and development of individuals with a rare syndrome. Inevitably, certain authors are cited often and study populations described repeatedly.

This systematic review aimed to present an overview of current developmental and behavioural manifestations in CdLS. We presented five areas of interest, namely developmental level, ASD, SIB, physical conditions, and medication use. The results show that assessment methods were heterogeneous, making comparison of presented results difficult. Improving our understanding of behavioural characteristics in CdLS requires more uniform methodology. We propose a criterion standard of instruments that can ideally be used in assessment of cognition, adaptive functioning, ASD, sensory processing, SIB, physical characteristics, medication use, and evaluating the context of individuals with a (rare) syndrome. This will improve understanding of behaviour in the context of developmental level and daily functioning. Combining a survey approach with direct in-person assessments is necessary to improve our in-depth understanding of behaviour in CdLS³⁰ and other (rare) syndromes.³ It may eventually lead to tailored, effective interventions to improve quality of life in individuals with rare syndromes.

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SUPPORTING INFORMATION

The following additional material may be found online:

Appendix S1: Key criteria included studies

Appendix S2: Key outcomes on behaviour (studies without standardized measurements are excluded)

Figure S1: Flowchart study selection

Table SI: Search strategy

Table SII: Summary of key study characteristics

Table SIII: Highlighting five areas of interest

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