CASE REPORT

Cornelia de Lange and Ehlers-Danlos: comorbidity of two rare syndromes

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SUMMARY

We present a case of a young adult with both Cornelia de Lange syndrome and Ehlers-Danlos syndrome. The patient showed non-verbal autism, intellectual disability and severe/intractable self-harming behaviours that led to a life-threatening complication (ie, septicaemia). A significant reduction in the self-harming behaviours was attained in a multidisciplinary neurobehavioural inpatient unit after addressing all causes of somatic pains, managing pain using level II and III analgesics, stabilising the patient's mood, limiting the iatrogenic effects of multiple prescriptions and offering a specific psychoeducational approach.

BACKGROUND

Cornelia de Lange syndrome (CdLS) is a rare multiple-malformation syndrome often associated with autism; intellectual disability (ID); and, more specifically, self-harming behaviours.[1 2] Some dermatological abnormalities may occur, such as cutis marmorata, the existence of a single transverse palmar crease and abnormal dermatoglyphics.[3] Mutations in one of the three known related genes (NIPBL, SMC1A and SMC3 genes) are identified in half of cases, but the diagnosis is clinical.[4 5] The classic type of Ehlers-Danlos syndrome (EDS) (a genetic connective tissue disease) is a rare disorder characterised by stretchy skin, abnormal wound healing, joint hypermobility, (sub)dislocated joints,[6] and chronic and acute pain.[7] We report, to our knowledge, the first case of a patient suffering from CdLS with comorbid EDS. We aim to describe how both disorders influenced the vicious cycle of self-harming behaviours, severe lesions and intense pain, leading to intractable self-harming behaviours and agitation that were finally improved through multidisciplinary management in a neurobehavioural unit.[8]

CASE PRESENTATION

A 21-year-old man was hospitalised in a neurobehavioural unit for a severe behavioural disorder, with self-harming actions, agitation and heteroaggressivity, after several psychiatric hospitalisations had not improved his condition. He presented CdLS with non-verbal autism and severe intellectual impairment, failure to thrive (4.76 feet tall, with a body mass index of 16.6 kg/m^2), characteristic facial dysmorphism (microcephaly, micrognathia, arched and confluent eyebrows (synophrys), anteverted nostrils, thin lips), osteoarticular complications requiring the use of a wheelchair (limb deformities, scoliosis, multioperated hallux valgus, amputation of a toe, brachymetacarpia of the first metacarpal, brachyphalangy, a fracture history of elbow and shoulder dislocations), gastroenterological abnormalities (gastro-oesophageal reflux disease, severe chronic constipation with episode of bowel obstruction), renal (acute pyelonephritis) and testicular abnormalities (a Sertoli cell tumour with large calcifying cells that required orchiectomy). He also presented EDS of the classic type, with a pale appearance of the skin, marked skin hyperextensibility, abnormal healing with widened atrophic cutaneous scars, joint hypermobility and haemorrhagic syndrome. Two of his first-degree relatives had a history of EDS. Proprioceptive pains were likely associated with his various traumatic wounds, bone and joint deformities.

Psychiatric assessment found a severe autistic syndrome (Children Autism Rating Scale (CARS) score=41), ID (Vineland-II standard score=31) and deviant communication; and obsessive-compulsive traits, irritability, intolerance to frustration, loss of interest in his repetitive behaviours and autistic preoccupations, and mood fluctuation, resulting in a depressive syndrome. Severe self-harming behaviours, including beatings and deep bites, despite wearing mittens and thick protective fabrics on the limbs, were compounded by the skin flap detachments and haemorrhagic syndrome of EDS. These behaviours required nursing care several times per day, and repeated emergency room and dermatology department visits (for controlled wound healing procedures, bandages and sutures; figure 1). We also assessed all possible organ comorbidities of both CdLS and EDS, requesting internal medicine advice for sepsis related to impairment of skin barrier and iron-deficiency anaemia (haemoglobin 6.7 g/dL), an ophthalmological consultation for subconjunctival haemorrhage, and surgical repair after repeating severe hallux bites, baring orthopaedic equipment (screws; figure 2).

INVESTIGATIONS

Given the high prevalence of genetic aetiology (nearly 30%) found in complex autism (meaning autism with comorbid malformative syndrome and/or dysmorphology and/or microcephaly),[9] genetic assessment of our patient had been performed in early childhood. CdLS was found, with a missens mutation (cDNA: 6274C→G) of the Nipped-B-like protein (NIPBL) gene located on chromosome 5 (5p13.2) affecting the protein sequence (Leucine 2092 Valine). Diagnosis of EDS, classic type was established by family history and clinical

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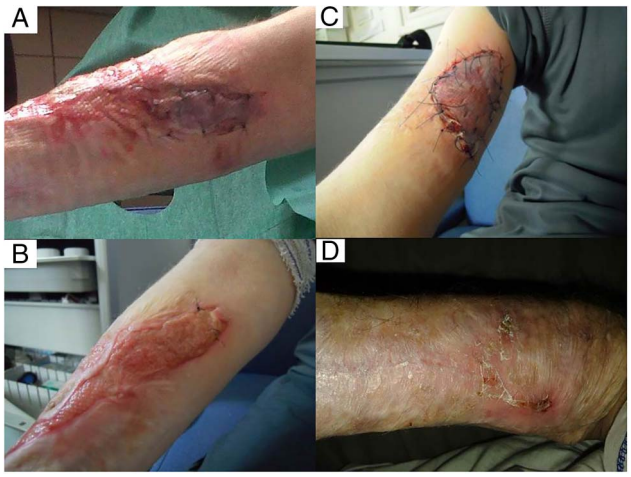

Figure 1 Skin lesions (bites) on arm at admission (A); skin lesions after controlled healing (B); stitching of the skin lesion (C); and healing of the wound (D).

examination based on the Villefranche nosology.[6] Studies of type V collagen chains are usually not useful in confirming a diagnosis, as approximately 50% of individuals with classic EDS have no identifiable pathogenic variant in *COL5A1* or *COL5A2*.[10] Thus genetic testing for classical EDS was not performed for this patient with typical signs.

The diagnosis of autism was confirmed by the Autism Diagnostic Interview—Revised (ADI-R) and clinical assessment. The CARS evaluated the degree of severity of autism.

All investigations were based on physical signs and clinical call points, in the absence of verbal language (additional tests of kidney and urinary tract due to urinary functional signs, genital surgery with anatomopathological examination after discovery of a suspicious testicular mass, complete blood count and internal medicine advice for suspected septicaemia, ophthalmological advice for eye haemorrhage and orthopaedic advice with foot X-ray for bloody hallux bites).

TREATMENT

Significant clinical improvement was observed (figures 1 and 3) after 3 months of hospitalisation involving both medical and psychoeducational treatment. Medical treatment included: (1) nursing and physical care involving management of pain with level II and III analgesics, and massages. Tramadol hydrochloride (300 mg/day) was used to relieve pain of skin wounds and

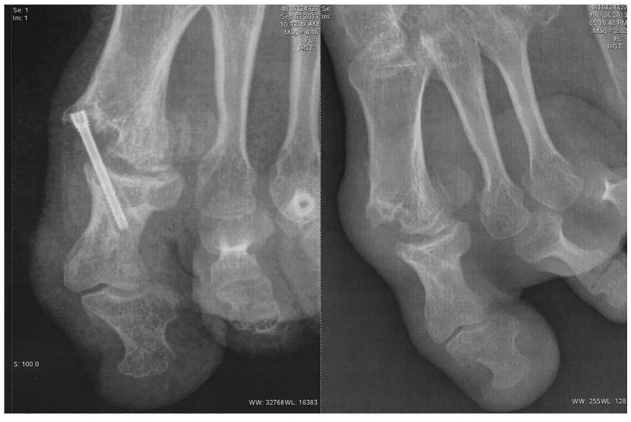

Figure 2 X-ray of the left foot before (left) and after (right) surgical ablation of screw.

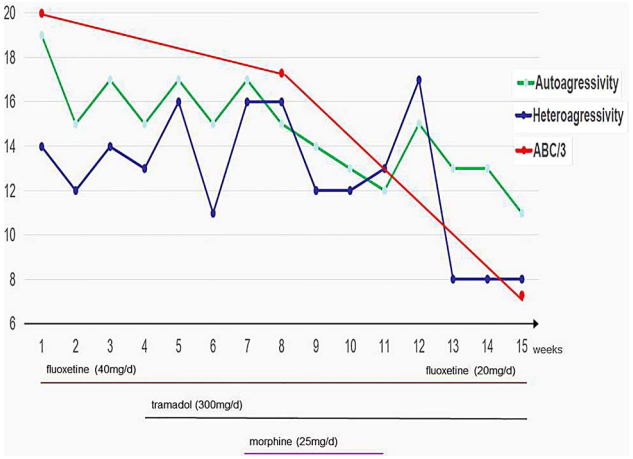

Figure 3 Improvement of clinical scales during inpatient stay (heteroaggression was based on the Hetero Aggressive Behaviour Scale; auto aggression was based on the Auto Aggressive Behaviour Scale; ABC=Aberrant Behaviour Scale).

chronic pain associated with EDS.[7] In addition, morphine oral solution 5 mg taken 5 times/day was used against acute pain due to displaced intra-articular screw and postsurgical pain.[11] Massages were also used as an additional strategy to deal with the chronic joint pain and muscle spasms in EDS.[7] (2) Prevention of the risk of intestinal obstruction by chronic constipation (frequent in autism,[12] and aggravated by antipsychotics[13] as well as by morphine[14]) using laxatives, sequential enemas and a decrease in antipsychotic drug use (used to reduce outpatient behavioural problems but without targeting their specific causes), and treatment of gastro-oesophageal reflux disease with antireflux and gastric-protective treatment. (3) Supplements for iron-deficiency anaemia. (4) Finally, decrease in rituals and irritability using a selective serotonin reuptake inhibitor (SSRI) (fluoxetine 20 mg/day), as SSRIs might be effective on these symptoms for adults with autism and comorbid depression.[15]

Psychoeducational treatment involved functional analysis of disruptive behaviours (focusing on the identification of variables that influence the occurrence of challenging behaviours), search for reinforcing factors (verbal and physical factors that could reward and encourage desired behaviour) and behavioural therapy targeting challenging behaviours. Initial use of protective equipment (a mesh helmet to prevent bites) helped to reduce the likelihood of bodily injury, and also reduced the sensory stimulation experienced during and after episodes of self-injurious behaviour. Thereby the protective equipment served as an extinction mechanism.[16] Use of non-verbal communication methods (Picture Exchange Communication System and Makaton) and positive reinforcement based on reinforcing factors[17] permitted an improvement in communication skills by decreasing deviant communication and inappropriate behaviours, and increased social initiations.

OUTCOME AND FOLLOW-UP

During the 2-years following hospital discharge, the patient only twice needed the emergency room services of his local hospital in order to manage brief disruptive behaviours, and he was hospitalised only once for 3 weeks to handle a shoulder dislocation associated with EDS joint hypermobility.

DISCUSSION

This report showed the association of two rare syndromes, CdLS and EDS, which, to the best of our knowledge, has never

before been reported in the literature. Our patient had a rare testicular tumour, described in neither CdLS nor in EDS, but occurring in 40% of cases in a dysgenic context.[18] The rest of the clinical picture met the expected phenotypes for both syndromes, and the severity of the case was related to the vicious cycle of self-harming behaviours related to CdLS, the severity of the pain related to EDS, the secondary complications of the painful lesions (anaemia, extreme agitation) and iatrogenic effects (multiple prescription of antipsychotics to control agitation).

Whatever the aetiological context, acute behavioural episodes in autism and ID can often be underpinned by a painful medical condition, and treated by a functional and multidisciplinary approach.[8 19 20] In the case of our non-verbal patient with autism due to a syndromic disease, the role of the psychiatrist was to target the main causes of the self-harming behaviours, including the causes of physical pain. We had to coordinate both specific somatic and psychoeducational treatment (such as functional analysis of disruptive behaviours, behavioural therapy targeting these challenging behaviours, using facilitated communication), as self-injurious behaviours may be caused not only by psychiatric but also by organic, painful, or environmental conditions.[8] Massages and gloves, and protective elbow and knee pad use could have played an antalgic role in producing tactile compressive stimulation of painful areas, with an inhibitory effect due to the application of gate control to the transmission of pain.[7] Pains in EDS are usually resistant to morphine and other painkillers.[7] We can presume our patient improved under morphine and tramadol treatment because of severe acute pain he presented from his displaced screw, then the postoperative pain. The ascertainment of depression was complicated by absence of language on the one hand, and phenotypic overlap between autism and depression on the other (by ways in which autistic symptomatology can mask cardinal features of depression, and by atypical manifestations of depression in patients with autism).[21] We proposed antidepressant treatment assuming a depressive syndrome in our non-verbal patient based on irritability, labile mood, loss of restricted interests and a very ritualistic mode of functioning, as it may occur in autism with depression.[22] It should be noted that comorbid depression is highly prevalent in young adults suffering from CdLS,[23] autism,[24 25] or health problems.[26]

Learning points

- Severe self-injurious behaviours associated with autism and/or ID can improve in inpatient neurobehavioral units with interdisciplinary collaboration.
- Patients with syndromic autism, given the high frequency of medical comorbidities, often benefit from inpatient care in specialised neurobehavioral units.
- The role of the psychiatrist is to target the main causes of self-harming behaviours, including all of the causes of physical pain, and to coordinate specific somatic and psychoeducational treatment.
- The use of symptom-dependent prescription of antipsychotics to control behavioural disorders should not be the only treatment, as it is associated with increased iatrogenic features (eg, bowel obstruction).

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Contributors CC, VG and AC collected the clinical details of the patient's report. SB collected the dermatological aspects and photographs. CC reviewed the literature. VG and AC revised the manuscript critically for substantial psychiatric content. All the authors have given final approval of the version to be published.

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