Cornelia de Lange syndrome – characteristics and laparoscopic treatment modalities of reflux based on own material

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Abstract

Cornelia de Lange syndrome (typus degenerativus amstelodamensis, CdLS, Brachmann syndrome) is a complex, congenital, multi-gene anomaly characterized by mental retardation. Its features include growth inhibition, hirsutism, structural anomalies of the limbs and abnormal development of osseous structures of the face. Independent of the phenotype of the disease, 85% of patients are assumed to have symptoms of gastroesophageal reflux disease (GERD). Aspiration pneumonia is one of the complications of GERD and a main cause of death in these patients. Patients not responding to medical treatment qualify for surgery. Until recently, anti-reflux procedures for GERD in CdLS patients were performed solely via laparotomy. The contemporary gold standard is a procedure performed laparoscopically. There are a few case reports of patients with CdLS operated on for GERD with laparoscopy available in the literature. The goal of this paper is to present two cases of Cornelia de Lange syndrome treated with laparoscopic antireflux procedures. We have performed two such procedures in 14 and 16 year-old girls with typical symptoms of the syndrome, i.e. developmental and mental retardation, hirsutism, structural limb anomalies and abnormal face development. The main indications for surgery in both cases were ineffective medical treatment and persistent aspiration pneumonia and its complications as a result of the gastroesophageal reflux. Oesophageal hiatus hernia and reflux were confirmed with accessory tests in both cases. During 36 months of follow-up, according to Barents, no episode of oesophageal reflux with acidic gastric content was noted. The treated children slept well during the night and did not need hospitalization for aspiration pneumonia. Neither of them required proton pump inhibitors. It should be concluded that laparoscopic Nissen fundoplication is a safe and effective method of GERD treatment in children with CdLS.

Key words: *Cornelia de Lange syndrome, gastroesophageal reflux disease, laparoscopic procedures.*

Introduction

Cornelia de Lange syndrome (typus degenerativus amstelodamensis, CdLS, Brachmann syndrome) is a complex, multi-gene inherited anomaly characterized by mental retardation. Growth retardation, hirsutism, structural anomalies within the limbs and aberrances in skull and face development are characteristic features of this syndrome. Eighty-five percent of these patients, regardless of the phenotype, are estimated to have symptoms of gastroesophageal reflux disease (GERD) [1-3]. Aspiration pneumonia is one of the complications of GERD and a main cause of death in these patients. Patients not responding to medical treatment qualify for surgery. Until recently, GERD in patients with CdLS was treated surgically with laparotomy. Now laparoscopy has become the gold standard. A few cas-

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es of CdLS patients treated with laparoscopy for GERD can be found in the literature [2, 4-11].

The aim of this study was to present two patients with CdLS treated with laparoscopic anti-reflux procedures. Two such procedures were performed in 14 and 16-year-old girls with classical syndrome symptoms, i.e. developmental retardation, hirsutism, structural anomalies of the limbs, mental retardation and facial anomalies. Unsuccessful conservative therapy and persistent aspiration pneumonia and its complications resultant from gastroesophageal reflux were the main indications for surgery. In each case hiatal hernia and reflux were confirmed with additional tests.

Case reports

Cornelia de Lange syndrome characteristics

The name of the syndrome comes from Cornelia Catharina de Lange, who described it in two girls, 6 and 17 months old, in 1933 in Amsterdam. At that moment, apart from characteristic features of the syndrome, aspiration pneumonia resulting most likely from GERD was diagnosed in both girls. The syndrome is sometimes called Brachmann syndrome after the German physician Winfried Brachmann, who described in 1916 a child with typical features of a disease described earlier. His report was based on a clinical examination and autopsy of a patient who died on the 19th day of life. The cause of death was pneumonia resulting most likely from gastroesophageal reflux. Cornelia de Lange syndrome is genetically determined and has several modes of inheritance: autosomal dominant, autosomal recessive, sex-associated and 'de novo' mutations. Approximately half of cases result from mutation of the NIPBL gene located on the 5th chromosome, which encodes a cohesin subunit – a complex that holds sister chromatids together during mitosis. This type of syndrome is called CdLS1. A sex-associated type called CdLS2 is caused by a mutation of the SMC1L1 gene located on chromosome X, encoding another subunit of this complex. Disease resulting from SMC3 gene mutation located on chromosome 10, also encoding a subunit of this complex, is called CdLS3 type. Altogether, CdLS occurs in 1 : 30 000 – 1 : 50 000 live births. Newborns with CdLS are usually small, although sometimes they can have a normal birth weight. In spite of their short stature (122-150 cm), they enter puberty at normal age. Developmental retardation, of various degrees, is another characteristic feature of the syndrome. Nearly all children with CdLS learn to walk, although those with the classic form of the syndrome may not be able to walk until the age of five.

In Poland there are 143 children diagnosed with CdLS registered with the CdLS Association – Poland, created in 2002. The goal of the Association is to find and integrate children with CdLS and their families in Poland, providing both group and individual care in specialized medical centres. Promotion of knowledge on the syndrome and securing access to educational material, protection of rights of children and their families in everyday life, coordination of integration, rehabilitation and care as well as societal, legal and medical help are the main activities of the association. Similar affiliations exist in the U.S., UK, Australia, Malaysia, New Zealand, Philippines, Singapore, Canada, Denmark, France, Belgium, Switzerland, Netherlands, Italy and Japan.

As mentioned, patients with suffer from severe gastroesophageal reflux with reflux episodes lasting several minutes to over an hour. It is accompanied by pain, manifesting as flex movements, cessation of food ingestion or even self-infliction. Some children present with increased appetite, as ingestion of certain foods neutralizes gastric acid and causes temporary relief of symptoms. Hence, early diagnosis of GERD and its effective treatment are fundamental for pain resolution. Symptoms attributable to gastroesophageal reflux are present in 60% of children in the CdLS Association – Poland and aspiration pneumonia occurs frequently, as in our two patients [12-14].

Crucial progress in treatment of gastroesophageal reflux was expected from the introduction of proton pump inhibitors (PPI) to the market. Despite their regular use some patients continue to suffer from pain and disease complications. These involve oesophagitis with massive haemorrhages to the gastrointestinal tract in 6-7% of patients, presence of erosions and ulcers, oesophageal stricture, severe asthma in 45-65% of cases attributable to reflux disease and – above all – aspiration pneumonia. A pre-cancerous abnormality called Barrett's oesophagus must also be remembered and it affects 5-15% of patients with gastroesophageal reflux. Patients with CdLS are at much higher risk than other patients. Endoscopic surveillance of the oesophagus is recommended in children with long-lasting reflux. These patients are qualified for surgery. The strategy of surgical treatment ought to be based on three basic rules, i.e.: release of typical subjective

symptoms, healing and prevention of reflux-dependent oesophageal mucosa injury recurrences, and prevention of long-lasting disease complications. Numerous anti-reflux procedures have been described, yet Nissen's method is now the most popular one and consists of formation of a loose pouch surrounding 360° of the abdominal part of the oesophagus (floppy Nissen) [2, 15-17]. Significantly smaller surgical trauma and short hospital stay after laparoscopic procedures led to application of this method in treatment of reflux disease in CdLS patients.

In our department two anti-reflux procedures with laparoscopic technique in patients with CdLS have been performed. Children unsuccessfully treated conservatively for at least 6 months with proton pump inhibitors were qualified for surgery.

Anaesthesia

The biggest problems appear when the method of anaesthesia of patients with CdLS must be chosen. It is difficult to work out a scheme of standard anaesthesia as these patients have numerous and various aberrations accompanying the syndrome. For this reason, according to the opinion of anaesthesiologists, not every patient can be anesthetized. Presence of parents is recommended from the moment of premedication until anaesthesia induction. Premedication is given immediately before entering the operative theatre (barbiturates – only in the presence of an anaesthetist; opioids – small doses intramuscularly approximately an hour prior to surgery; ketamine – intramuscularly or intravenously with atropine; benzodiazepines should not be used). In anaesthesia induction ketamine with atropine was used. Adequate intubation conditions at inhalation anaesthesia can be achieved with sevoflurane. Difficulties related to short neck, neck rigidity, gothic palate or cleft palate can be encountered on intubation. At any instrumental intubation availability of a bronchofibroscope is recommended. Relaxation of skeletal muscles is necessary, as for any laparoscopic procedure. Proper qualification for anaesthesia, meticulous assessment of conditions for intubation, proper preoperative preparation and intraoperative management allow minimization of risk of anaesthesiological complications [18-21].

Based on the opinion and experience of others, in our team of surgeons and anaesthesiologists, we have worked out a way of preparation for surgery and anaesthesia. Routine laboratory tests and radiological studies necessary for the procedure were performed. One patient needed placement of a central IV catheter. Intravenous premedication in the operative room consisted of 0.1 mg atropine, 20 mg of ketamine, and 25 mg of thiopental. Pre-oxygenation was continued for 5 min with 100% oxygen and inhalation induction achieved with 8 vol% sevoflurane administered for 5 min. Intubation was performed when the patient was still breathing and the position of the tracheal tube was checked. Then, relaxation of skeletal muscles was achieved with cisatracurium and mechanical ventilation with a mixture of 400 ml of O_2 and 100 ml of atmospheric air with 1.6 vol% sevoflurane in exhaled air in a minimal flow closed circuit was installed. Later, fentanyl was administered according to heart rate and blood pressure. Heart rate, blood pressure, oxygen saturation, $ETCO_2$, body temperature, concentration of oxygen, sevoflurane and CO_2 on inspiration and expiration were monitored. After surgery, spontaneous recovery of neuromuscular responsiveness occurred and the patient was extubated when responsive to verbal stimuli. Pain control was achieved with 250 mg of paracetamol given per rectum every 6 h on the first postoperative day. Both patients were discharged home on the 2nd postoperative day.

Surgical technique

Surgical procedures were performed after typical preparation and anaesthesia (described above). Patients were placed in a supine position with legs apart. In spite of anatomical anomalies, positioning of the patients did not cause any technical problems. After pneumoperitoneum was inflated to 10 mmHg,

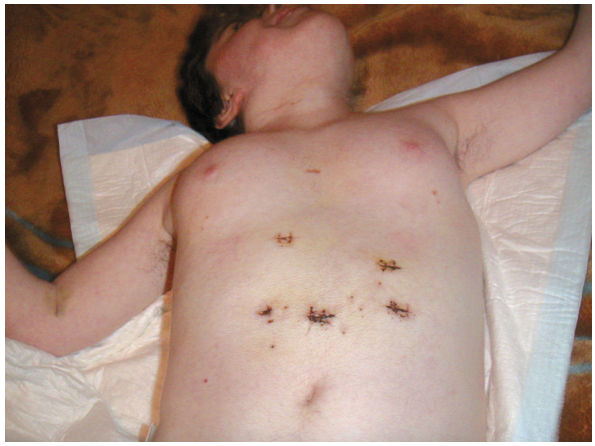

Figure 1. State after operation

the operative table was repositioned to Fowler's position, which resulted in the bowels being pulled downwards from the operative field by gravitational force. The operator remained between the legs of the operated patient. Other personnel and equipment were located in a typical way. No technical difficulties were noted because of anatomical restraints of the patients. A 10 mm visual port was placed above the umbilicus in the midline, at one third of the distance from the umbilicus to the xiphisternum. A 10 mm working port was placed slightly higher and to the right of the visual port, while an accessory 5 mm trocar was placed immediately below the xiphoid. Two other 5 mm trocars were placed slightly higher to the left than the visual port and under the left costal arch (Figure 1). Inspection of the peritoneal cavity revealed broad splitting of the diaphragmatic crura with visible hiatal hernia. No other abdominal pathology was found. After typical liberation of the gastric fundus and isolation of the oesophagus with LigaSure apparatus, diaphragmatic crura were sutured with 2-0 suture, followed by regular Nissen fundoplication. Control of haemostasis, deflation and closure of the wounds ended the procedure. Patients were released home on the second postoperative day.

Postoperative follow-up

No complications were seen in the post-operative period. According to parents' reports, during 36-month follow-up no incidents of regurgitation with acidic gastric content into the oesophagus were noted. Treated patients showed no signs of psychomotor excitation during night time, as was seen prior to surgery. Neither of the patients was hospitalized for aspiration pneumonia during the whole follow-up, nor did they require administration of proton pump inhibitors.

Conclusions

Laparoscopic Nissen fundoplication can be considered a safe and effective method of operative treatment of GERD in children with CdLS. Within 3-year follow-up no recurrence of the disease was seen in the treated patients and nor were there any complications. These two factors contributed significantly to improvement of life quality. The technique of the procedure is not very different from typical surgery of this kind. However, anomalies characteristic of the syndrome call for increased vigilance in both the preoperative period and anaesthesia, and potentially may necessitate modification of the procedure technique.

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