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Neurophysiological changes and chronic pain in cleft patients

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ABSTRACT

The aim of this study was to evaluate if patients after orofacial cleft repair experience neurophysiological changes with consecutive chronic pain states after surgery.

Patients (n = 48) with a repaired orofacial cleft (CLP) recruited in a support group took part in a survey including five questionnaires. They revealed pain states, described cleft situation and history, and epidemiological data. Patients' quality of life and psychological comorbidity after the surgical procedures were assessed with the Oral Health Impact Profile (OHIP), the Giessen Subjective Complaints List (GSCL) and the Hospital Anxiety and Depression Scale (HADS). Furthermore, psychosocial impairment was documented.

39 out of 48 subjects with CLP reported to have experienced pain during the last 6 months. Pain was proven to be already chronic for 36 persons. Locations of pain were the orofacial region, back and limbs. Neurophysiological perception to cold, warmth, pressure and touch were found to be inhomogeneous.

Local disturbances of subjective sensitivity in hard and soft tissues in the operated region are suspicious for neuropathic disorders and peripheral and central sensitization. 16 participants also reported that during dental interventions higher doses of local analgesia were necessary to achieve a pain free condition. Overall participants with CLP demonstrated elevated levels for anxiety and depression.

As a conclusion for daily routine, CLP patients are considered to be at a higher risk to develop chronic pain states. To avoid these, proper pain and psychological management must be performed from early childhood. Further clinical studies examining patients with neurophysiological diagnostic tools are needed.

1. Introduction

Early childhood surgery can result in long-lasting neuronal changes (Saps and Bonilla, 2011). Thus, due to tissue injury, postoperative disturbances of peripheral somatosensory perception can occur, leading to generalized pain sensitization (Schwaller and Fitzgerald, 2014). Hermann et al. reported that neonatal pain experiences might have an impact until school age (Hermann et al., 2006). Schwaller and Fitzgerald (Schwaller and Fitzgerald, 2014) hypothesized that long-lasting changes in pain sensitization are caused by increased sprouting of nerve endings, sensitization of the spinal cord, neuroimmune effects and the loss of inhibitory neurons. Cleft lip and palate malformations require several surgical interventions in early childhood. Reportedly, oral health of children with clefts had a statistically significant impact on oral health-related quality of life compared to a group of non-affected children (Rando et al., 2018). As seen in our cohort and in conformity with other published data (Hermann et al., 2006), persistent central hypersensitivities may result. Patients report postoperative pain after reconstruction of alveolar bone defects (Andersen et al., 2014) and generalized pain sensitivity results. These neurophysiological changes can persist into adulthood.

In the treatment of acute postoperative pain, frequent pain monitoring and a multimodal approach is essential in these paediatric patients (Milchak et al., 2017). Guidelines for postoperative pain management are still missing (Reena et al., 2016).

Subjective morbidity after reconstruction was objectified by using a representative normalized questionnaire (Fasolis et al., 2012; Andersen et al., 2014). In the literature, various tools for measuring quality of life in patients with different clefts have been

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established (Chang et al., 2017a; Irace et al., 2018). Patient Reported Outcome Measures (PROMs) were able to evaluate reconstructive outcomes in cleft lip/palate patients after secondary alveolar bone grafting compared to a control group (Chang et al., 2017b).

In a German survey, 56.1 % of contacted persons of a representative cohort finished the study of which 32.9 % reported chronic pain (Häuser et al., 2013). Within the population of patients with cleft lip and palate (CLP), the reported prevalence is often reduced to temporomandibular disorders, despite those patients are undergoing an abundance of surgical, orthodontic, logopaedic and otorhinolaryngologic interventions, starting within the first days of life. The aim of this epidemiological study was to explore the prevalence of neurophysiological changes and chronic pain in participants with CLP.

2. Materials and methods

Acquisition of data was performed after informed consent and in accordance with the ethical principles of the World Medical Association 2013 Declaration of Helsinki. By using an epidemiologic human study design, this study was independently reviewed. This study is in accordance with the appropriate International Ethical Guidelines for Epidemiological Studies.

2.1. CLP group

Participants were recruited according to the following principles:

For data collection, individuals were contacted anonymously by the self-support group of the Wolfgang Rosenthal Society. Participants with appropriate knowledge of German for informed consent and above 18 years of age were included. Individuals with an untreated cleft were excluded.

After patient consent, individuals were then contacted again by the Department of Oral and Maxillofacial Surgery of the University Medical Centre of the Johannes Gutenberg University of Mainz.

2.2. Questionnaires

Questionnaires were approved by the Institute of Medical Biostatistics, Epidemiology and Informatics (IMBEI), University medical centre of the Johannes Gutenberg University of Mainz. The analysis consists of five questionnaires, investigating symptoms over the past six months.

1) A questionnaire gathering epidemiological data (developed for this study)

The questionnaire was based on epidemiological concerns including 5 questions regarding family state, degree from school/college/university, job, age, gender, month of birth and year and signature date.

2) CLP questionnaire (developed for this study)

This questionnaire described the type/localization of the cleft, oral- and maxillofacial surgical treatments, psychological, orthodontic and otolaryngeal treatments, measured satisfactory surgical results concerning aesthetics, number of surgical treatments, age at primary reconstruction and genetics with clefts (family relationship).

3) Pain questionnaire (developed for this study)

Evaluation of neurophysiological changes at the surgical site experienced by the individuals, chronic pain states and localization, intensity, duration and frequency. In detail, Question 1 addresses reactions of the teeth at the cleft region compared to unaffected teeth. Thermal and mechanical neurophysiological changes had to be documented (Hyperalgesia – normal sensitivity – Hypoalgesia). Question 2 and 3 were similar for face and sensitivity concerning local anaesthesia. Questions 5–18 revealed pain states (localization, strongest pain: 0 = no pain –10 = unbearable, duration, frequency, medication, diagnosis, sleeping conditions, impairment of social life and job). Questions 19–20 described other physical restrictions and chronic pain disorders.

4) Hospital Anxiety and Depression Scale – German Version (HADS-D) (Herrmann and Snaith, 1995)
5) The Giessen Subjective Complaints List (GSCL) (Brähler et al., 2008)

2.3. Statistical analysis

The statistical analysis was performed by one data coder using IBM® SPSS® Statistics version 12.0 for Windows®. Data interpretation and analysis were performed by IMBEI, Mrs. Dipl. Math. Irene Schmittmann). Analyses concerning calculation of the absolute frequencies for the categorical features were included.

3. Results

Of n = 130 individuals contacted initially, n = 59 agreed to take part in the study. Finally, 48 volunteers sent questionnaires back to the investigators for analysis.

1) A questionnaire gathering epidemiological data (developed for this study)

The questionnaire was able to organize all epidemiological concerns. CLP patients were female (n = 36) and male (n = 12) with a median age of 44 years (female with a range of 28–67 years, male with a range of 33–64 years). Most of them (n = 29) were married, n = 13 single and n = 6 divorced. Evaluation of graduation degrees showed no degree in one case, secondary school (9 grade) in n = 4, secondary school (10 grade) in n = 12, and 11 patents graduated from high school. N = 20 went to university. Regarding occupational state, n = 21 worked full-time n = 12 part-time, 6 were unemployed and n = 3 were homemakers. N = 3 were pensioners and n = 1 was disabled. No epidemiological data showed a special risk to develop chronic pain states (see Table 1).

2) CLP questionnaire

The majority n = 34 had a complete cleft lip and palate, n = 13 an incomplete cleft and one patient an oblique facial cleft. The incomplete clefts presented as isolated cleft lip (n = 3), cleft lip and alveolar process (n = 3) and cleft palate (n = 7) (Table 2).

All individuals had surgical closures of the cleft, with lip reconstruction (LR) being the most frequent procedure (n = 40). Often additional corrective surgeries and other treatments were necessary (Table 3). 42 participants underwent orthodontic treatment; 20 with removable appliances and 1 individual with a fixed

Table 1
Epidemiological data. Gender, age, marital status, graduation and occupation of the study participants.

gender	
female	36
male	12
age (median 44 years)	
female	28–67 years
male	33–64 years
marital status	
single	13
married	29
divorced	6
graduation	
no degree	1
secondary school (9 grade)	4
secondary school (10 grade)	12
high school	11
university	20
occupation	
full-time work	21
part-time work	12
unemployed	6
housewife/-man	3
pensioners	3
disabled	1
other information	2

Table 2
Kind of cleft.

lip clefts	
left	2
right	1
bilateral	
not specified	
lip + alveolus clefts	
left	1
right	2
bilateral	
not specified	
palate clefts	
left	
right	1
bilateral	4
not specified	2
lip + alveolus + palate clefts	
left	15
right	2
bilateral	16
not specified	1
oblique facial clefts	
left	
right	
bilateral	
not specified	1

Table 3
Cleft repair.

cleft lip repair	40
cleft palate repair	39
velopharyngoplasty	15
alveolar bone grafting	21
corrective surgery (lip, columella, vestibulum)	31
septorhinoplasty	26
orthognathic surgery	13
dental implant	3
paracentesis	1
tympanostomy tube	3
other surgery	6

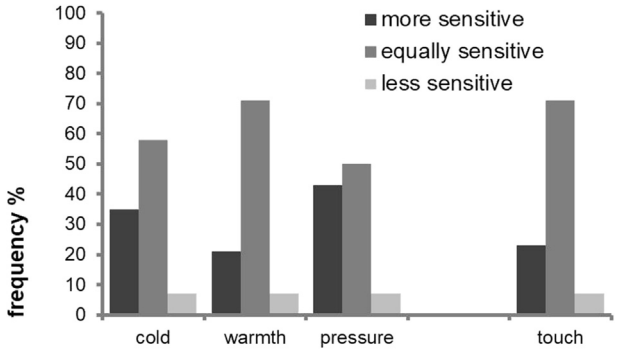

Fig. 1. Subjective sensitivity in the hard and soft tissues in the cleft region. Subjective sensitivity to cold, warmth and pressure of teeth in the area of the cleft compared to the healthy area as reported by the participants (cold, warmth, pressure). Subjective sensitivity of the skin nearby the cleft compared to the healthy area as reported by the participants (touch).

appliance. n = 21 had both. 26 participants underwent psychotherapy.

3) Pain questionnaire

Fig. 1 shows the subjective sensitivity in the hard and soft tissues in the cleft region compared to the healthy area in CLP subjects. The teeth beside the cleft were more sensitive to cold in 15 persons. 25 persons considered the teeth beside the cleft to be comparably sensitive and 3 persons as less sensitive against cold. Similar perceptions were experienced for warmth. 9 persons had the experience of a higher sensitivity against warmth. 30 persons considered the teeth beside the cleft to be equally sensitive and 3 persons as less sensitive to warmth. To pressure in 18 persons the teeth in the cleft area were more sensitive, for 21 persons equal and for 3 persons less sensitive. The skin near the cleft was more sensitive in 10 persons, in 31 persons similarly sensitive and in 3 persons less sensitive than experienced at the other side.

16 participants also reported that during dental interventions higher amounts of a local anaesthetic were necessary to achieve a pain free condition.

39 subjects with CLP reported to have experienced pain in the last 6 months and 11 specifically in the operated region. Of those, 23 suffered from pain for more than five years, 10 persons for more than one year and 3 persons for more than 6 month (Fig. 2A). This means, the pain is already chronic for 36 persons. Of the 36 people who suffered from chronic pain, 28 were female and 8 were male. Concerning the frequency of pain episodes, 14 participants suffered constantly, 7 once or twice a week, and 13 once or twice a month (Fig. 2B). For the 39 participants with CLP having pain over the last 6 months, pain intensities differ from 1/10 to 10/10 (Fig. 2C).

The prominent locations of pain were in the orofacial region (9 persons), the head (8 persons), the back (11 persons) and the limbs (10).

Medication was needed constantly in 2 persons with CLP having pain within the last 6 months. 6 persons often needed medication and 15 persons only sometimes. Predominantly, NSAID's were the drugs of choice. Furthermore, psychosocial impairment was documented in 27 of the participants (Fig. 3A) and insomnia in 26 of the participants with CLP had pain within the last 6 months (Fig. 3B). Incapacity for work due to pain was documented in 18 participants of the participants with CLP having pain within the last 6 months.

4) Hospital Anxiety and Depression Scale – German Version (HADS-D)

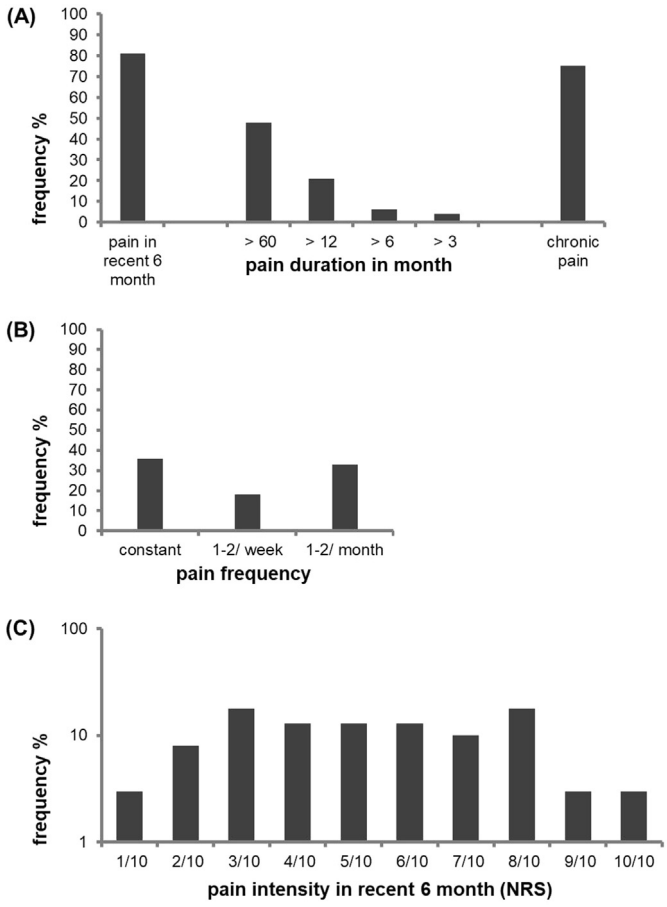

Fig. 2. Pain experience. **(A)** Pain experience in the last six month/Pain duration in month/chronic pain. **(B)** Pain frequency in the last six month. **(C)** Pain intensity in the last six month (numeric rating scale (NRS)).

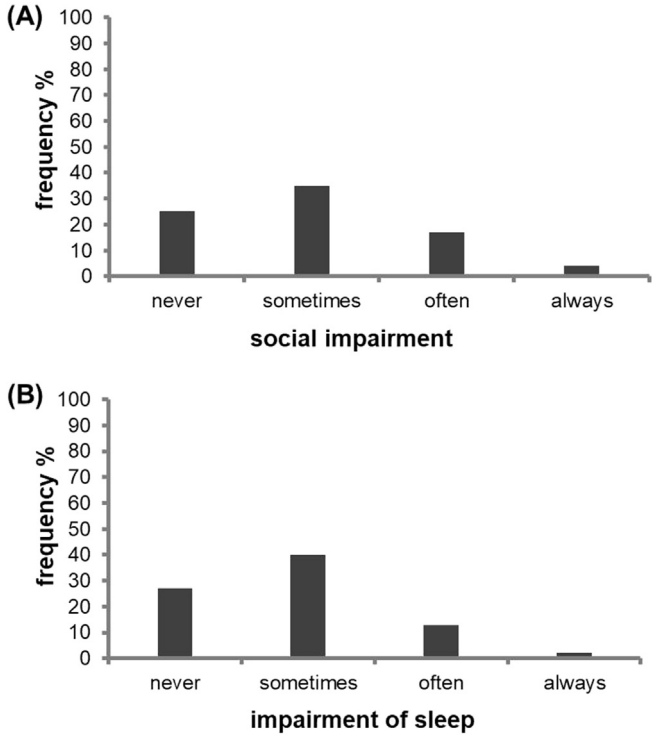

Fig. 3. Impact of pain. **(A)** Social impairment. **(B)** Insomnia.

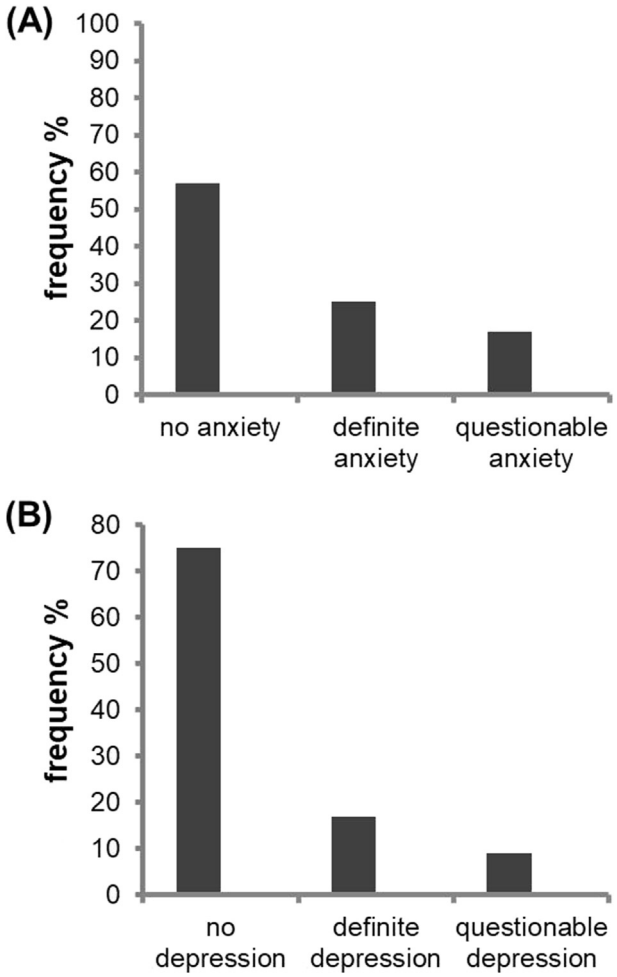

Fig. 4. Evaluation of HADS-D. **(A)** Anxiety. **(B)** Depression.

Overall, individuals with CLP demonstrated elevated levels of anxiety disorders. 12 participants showed positive anxiety levels (>11) and 8 participants levels from 8–10, where an increase in anxiety level is uncertain (Fig. 4A). Depression levels were elevated (>11) in 8 participants and uncertain (8–10) in 4 participants (Fig. 4B).

5) The Giessen Subjective Complaints List (GSCL)

Evaluation of medical complaints revealed, compared to the general population, an increased tendency of exhaustion in 27 cases of the participants with CLP. 19 participants with CLP reported an increased tendency to suffer from stomach problems, 28 participants from rheumatic pain and 18 participants from heart complaints. 21 participants reported suffering from an increased level of discomfort.

4. Discussion

Reconstruction of orofacial clefts frequently includes complex reconstruction and repetitive surgical interventions. Often several additional corrective surgeries, pharyngoplasty, osteoplastic reconstruction and dental implants were necessary. Furthermore, 88% of the participants needed orthodontic treatments. Adjacent tissue and nerve damage with consecutive acute and chronic pain sensations are a major complication in the follow-up period.

Sensory disturbances remain a persistent problem in cleft patients. This may be either at the donor site of osseous grafts or at the cleft side. One study reported 5.6% persistent sensory disturbances at the donor site associated with symphyseal bone grafts (Andersen et al., 2014). Others describe 4.9% associated with iliac crest bone graft (Fasolis et al., 2012). In this study, neurophysiological perception to cold, warmth, pressure and touch were found to be inhomogeneous. Hypersensitivity was described as well as hyposensitivity regarding all parameters. Participants also reported that during dental interventions higher amounts of local anaesthetic were necessary to numb the tissues. These findings together may indicate sensory changes of neuronal pathways because of various surgical interventions since the 6th month of life. Studies (Fitzgerald et al., 1989; Li and Baccei, 2011) proved that the central nervous system may develop hypersensitivity after tissue damage in newborns. Objective analyses in this field are missing and must be completed with clinical assessments including Quantitative Sensory Testing (Rolke et al., 2006a, 2006b) which was found to be suitable in the evaluation of neurophysiological changes in various oral-/and maxillofacial indications (Said-Yekta et al., 2012; Hartmann et al., 2017a, 2017b). Consequently, local disturbances in subjective sensitivity in hard and soft tissues in the operated region are suspicious for neuropathic disorders and peripheral and central sensitization in these subjects as long-term effects of early and multiple treatments. To the best of our knowledge this is the first study that describes neurophysiological changes in cleft patients.

This study has also shown that there is a high rate of chronic pain (>3 months) in people with CLP (75%). Compared to chronic pain states in a German representative cohort (33%) (Häuser et al., 2013), this study shows that there is a higher level of pain prevalence in individuals who underwent cleft surgery.

Specifying the area of complaint, chronic back pain (not distinguished in segments like upper and lower back or coccydynia) was found to be reported in participants with CLP and non-affected ones. In a large representative population in Germany, the most common pain localization was found to be in the back (Häuser et al., 2009). In France, 38.3% of adults described chronic back pain. Husky et al. reported some factors affecting the distribution of chronic back pain such as female gender, older age, lower education, manual labor occupation and population density (Husky et al., 2018). In this study, the frequency of pain in the orofacial region was comparable to frequency of pain in the head and back, although more pain in the orofacial region was assumed because of the proximity to the surgical site. Therefore, back pain – either specific or non-specific - is proven to be a severe pain condition as shown in several other studies (Potthoff et al., 2018; Morton et al., 2019).

Chronic temporomandibular disorders were not the main complaint of the CLP subjects although many of the adult subjects with reconstructed CLP still have occlusal and functional abnormalities (Welte-Jzyk et al., 2018).

In a previous study, women showed a higher rate of chronic pain. The high rate of chronic pain in CLP females in our cohort might be associated with cleft reconstruction. Another study (Rando et al., 2018) showed no correlation with gender with impact on oral health-related quality of life in patients with clefts. In general, the prevalence of pain is known to be higher in women than in men and they report higher levels of pain after invasive procedures (Fillingim et al., 2009).

Correlation between pain and psychological changes in behaviour are well-documented: Dickens et al. (2002) noted in patients with chronic back pain (>6 month) higher anxiety (54%) and depression (31%) scales. Ohayon and Schatzberg (2003) found a positive relationship between chronic pain disorders (joint/articular, limb or back pain, headaches or gastrointestinal diseases) and higher depression scales. The psychological status showed significantly more anxiety than depression (Welte-Jzyk et al., 2018). In general, the CLP subjects showed higher subjective complaint scores including insomnia and social impairment. This is in accordance with Brand et al. (2009) who evaluated participants with CLP showing that they are six times more likely to report interactional social difficulties. They also observed no unfavourable sleep pattern with the presence of CLP. Analysis showed a significantly higher anxiety scale in the experimental group. This is in accordance with Means-Christensen et al. (2008) who reported relationships among pain, anxiety, and depression in primary care. In the cleft-free German population, chronic pain with associated physical and social impairments was reported in 5.4 % and associated with physical, mental and social impairments (2.3%) (Häuser et al., 2013). Therefore, clinical routine shows an underreporting of chronic pain by patients. Perhaps other difficulties (e.g. functional impairment and poor oral hygiene) caused by the malformation are more causative. In several studies, cleft patients have been described to have poorer oral health when compared to non-cleft persons (Rodrigues et al., 2018, 2019). Cleft patients are also known to have changes in their oral physiology diminishing the self-cleansing ability of individual saliva and microflora. Consequently, poor oral hygiene will consecutively lead to more dental treatment or more pain when missing regular appointments. Visiting the dentist on a regular basis might reduce pain in these patients. Further efforts should be made to establish standardized prevention and control programmes in CLP children (Rodrigues et al., 2019). A cleft toothbrush showed good effects (Rodrigues et al., 2018) and the surgical correction of CLP itself enhances self-cleaning ability and better compliance in maintaining oral hygiene in children as age advances (Pandey and Pandey, 2005). These factors may also help to reduce pain.

Nevertheless, there may be some possible limitations in current study. First, the study focused on cleft patients of a self-support group without a control group. Although we were able to draw conclusions based on a large representative population of the German society based on the survey of Häuser et al., results have to be interpreted with caution. Future research should evaluate cleft patients in a clinical setting and compare them to a matched control-group. A larger sample size should be included and evaluated in future studies.

Modern surgical techniques should aim to include adequate perioperative pain management. Frequent pain monitoring, a multimodal approach and perioperative analgesics are proven to be important in patients with clefts (Milchak et al., 2017). It is likely that of missing accreditation of various analgesics and medication for total anaesthesia, a high level of off-label usage was part of daily practice. On the other hand, children, especially of former times, might not have received correct pain management.

Another essential point is the informed consent of patients and parents. The understanding of the surgical procedures is highly correlated to patients' satisfaction with results (Andersen et al., 2014), parents' anxiety and the development of chronic pain states. Highly anxious parents are known to have a greater risk for inducing higher postoperative pain complications in infants and toddlers undergoing elective craniofacial surgery (Rosenberg et al., 2017). Standardized perioperative instructions increased patient adherence and it is tempting to assume a subsequent better outcome (Chang et al., 2017a). Chronic pain states were documented in 28% after iliac crest bone graft (Fasolis et al., 2012). Another study documented low levels of postoperative pain after iliac bone grafting procedures (Chang et al., 2017a). Although studies provide a large variety of treatment modalities for cleft

patients - depending on type of the lesion and other factors – results are still incomplete. Special techniques – like bone graft substitutes - may help to reduce impairment and chronic pain states (Liang et al., 2018). Other studies revealed patients' high tolerance level for mandibular symphyseal bone grafts (Andersen et al., 2014) or high satisfaction level with iliac crest bone graft (Fasolis et al., 2012).

5. Conclusion

A common complication after CLP reconstruction remains constant or frequent pain for long periods, leading to a large use of pain medication, frequent consultation of doctors and social and general health impairment.

The data show, that patients with CLP are at a higher risk of developing chronic pain, in which neurophysiological changes persist over years after cleft surgery. Therefore, employing the earliest possible preventive measures as appropriate for surgical treatment is advised. Perhaps adequate treatment guidelines could relieve a great amount of physical, psychological and social suffering.

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Appendix A. Supplementary data

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