Prague Medical REPORT

(Sborník lékařský)

Multidisciplinary Biomedical Journal
of the First Faculty of Medicine,
Charles University

Vol. 119 (2018) No. 4

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The Effect of Sensory Innervation on the Inorganic Component of Bones and Teeth; Experimental Denervation – Review

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Received May 9, 2018; Accepted January 31, 2019.

Key words: Bone innervation – Chemical elements – Sensory denervation – Laboratory rat

Abstract: The effect of the nervous system on bone remodelling has been described by many studies. Sensory and autonomic nerves are present in the bone. Immunohistochemical analysis of the bone have indicated the presence of neuropeptides and neurotransmitters that act on bone cells through receptors. Besides carrying sensory information, sensory neurons produce various neuropeptides playing an important role in maintaining bone and tooth pulp homeostasis, and dentin formation. Bone tissue and teeth contain organic and inorganic components. Bone cells enable bone mineralization and ensure its formation and resorption. Studies focused on the effects of the nervous system on the bone are proceeded using various ways. Sensory denervation itself can be achieved using capsaicin causing chemical lesion to the nerve. Surgical ways of causing only sensory lesion to nerves are substantially limited because many peripheral nerves are mixed and contain a motor component as well. From this point of view, the experimental model with transection of inferior alveolar nerve

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https://doi.org/10.14712/23362936.2019.1

is appropriate. This nerve provides sensory innervation of the bone and teeth of the mandible. The purpose of our paper is to provide an overview of the effects exerted by the nervous system on the inorganic component of the bone and teeth, and also to present an overview of the used experimental models. As we assume, the transection of inferior alveolar nerve could be reflected in changed contents and distribution of chemical elements in the bone and teeth of rat mandible. This issue has not been studied so far.

Introduction

Bone remodelation is a process that goes on throughout the life. This process is slow and is ensured by several hormonal, paracrine/autocrine, mechanical and transcription signals whose targets can be osteoclasts and osteoblasts at various stages of their lifespan. Defects in bone remodelation caused by imbalance between osteoblast and osteoclast activity lead to the development of osteoporosis or osteopetrosis. Both these cases are associated with risk of fractures (Elefteriou, 2005). Various studies of the effects of the nervous system on bone metabolism (Konttinen et al., 1996; García-Castellano et al., 2000; Elefteriou, 2005, 2008; Patel and Elefteriou, 2007; Lerner et al., 2008; Sample et al., 2011; Elefteriou et al., 2014; Wu et al., 2016) and tooth metabolism (Jacobsen and Heyeraas, 1996; Fristad, 1997; Byers et al., 2003; Standring, 2016) have been published. Besides carrying sensory information, sensory neurons also produce various neuropeptides, which play an important role in maintaining bone homeostasis (Wu et al., 2016). Additionally, neuropeptides influence the maintenance of homeostasis in tooth pulp and in dentin formation (Standring, 2016). For example, impact of a transection to inferior alveolar nerve (IAN) on the healing of an alveolar defect and its mineralization has been described in connection with the mandible (Lv et al., 2014). Other authors have published the effect of a lesion to IAN on dentin formation in the first molar in the rat (Jacobsen and Heyeraas, 1996). Bone tissue and teeth (enamel, dentin and cementum) contain an organic and inorganic component (Abou Neel et al., 2016). Calcium is one of essential elements in bones and teeth where it is found predominantly in the form of hydroxyapatite, which also contains phosphorus (Dermience et al., 2015). Calcium metabolism disorders manifest as changes in the structure and properties of bone mass and teeth. Calcium homeostasis is maintained by the activity of osteoclasts, which resorb the bone, thereby increasing serum calcium concentration, and by the concurrent activity of osteoblasts, which are involved in new bone mass formation, thereby decreasing serum calcium concentration (Wilhelm, 2007). Studies of the effects of the nervous system on bone tissue and teeth use various experimental models (Stewart, 1965; Retief and Dreyer, 1969; Torneck and Harnett, 1971; Hoffman and Tade, 1972; Hill et al., 1991; Apel et al., 2009). The purpose of this paper is to present an overview of the effects of the nervous system on the inorganic component of bone tissue and teeth. We assume that the transection of IAN could be reflected in changed contents

and distribution of chemical elements in the bone and teeth in the rat mandible. This problem has not been studied so far. At the same time, another purpose is to provide an overview of used experimental models.

Innervation of bone tissue and teeth

In the first decades of the 20th century, common histological techniques were used to demonstrate the presence of nervous fibres in the periosteum and in the bone. More precise imaging of bone innervation was allowed only with the onset of immunohistochemical analysis. Sensory and autonomic nerve fibres are found in the bone. The pathways of nerve fibres are related specially to blood vessels. More fibres are found in the epiphysis compared to the diaphysis. Branches of periosteal nerves enter cortical bone usually with blood vessels, at the place of Volkmann canals. In the bone the nerves continue in the Haversian canals. These nerves enter the bone marrow and provide rich innervation the osteochondral junction of the growth plate (Lerner et al., 2008). The direct contact of nerve fibres with bone cells indicates the meaning of innervation for the function of bone cells (Chenu, 2004).

Immunohistochemical analysis of the bone have shown the presence of neuropeptides and neurotransmitters in bone tissue. Evidence of the following has been found in the bone with respect to the sensory system for example: substance P and CGRP (calcitonin gene-related peptide). Representative of the autonomic system is for example VIP (vasoactive intestinal peptide). The nervous system can exert an action on the bone metabolism through the presence of receptors on osteoclasts and osteoblasts (Lerner et al., 2008).

Neuropeptides such as CGRP and substance P are synthesized in sensory ganglions, and they distribute both centrally and in the peripheral tissue (Yamashiro et al., 2000). CGRP stimulates osteoblast proliferation (Cornish et al., 1999; He et al., 2016). Additionally, a potential effect on osteoclast differentiation and function has been described (Hara-Irie et al., 1996; He et al., 2016). The results of some studies support the hypothesis that CGRP inhibits bone resorption *in vitro* (Zaidi et al., 1987; Akopian et al., 2000). Nerve fibres containing substance P and CGRP usually enter the bone along blood vessels. At some point they separate and terminate as free nerve endings in the bone marrow. Cortical bone is innervated to a lower extent (Elefteriou, 2005). Blood vessels and nerve fibres enter teeth through the root canal and reach up to the crown part (Lüllmann-Rauch, 2012). Tooth pulp is innervated by sympathetic nerves (which controls vasoconstriction); these nerves enter together with arterioles and sensory nerve fibres, which form a plexus below the odontoblast layer, and continue further to the layer of odontoblasts and dentinal tubules (Standring, 2016) as free nerve endings (Fristad, 1997). The nerve supply of the dentin-pulp complex is mainly made up of A fibres (both delta and beta) and C fibres. They are classified according to their diameter and their conduction velocity. The A fibres are mainly stimulated by an application of cold, producing sharp pain, whereas stimulation of the C fibres produces a dull aching pain. Because

of their location and arrangement, the C fibres are responsible for referred pain (Abd-Elmeguid and Yu, 2009).

Nerve terminals present in the pulp release various neuropeptides that have an effect on the homeostasis (Fristad, 1997; Byers et al., 2003; Standring, 2016). As reported by Jacobsen and Heyeraas (1996), neuropeptides such as CGRP and substance P are involved in the formation of dentin.

The inorganic component of bones and teeth

The bone contains 45% of mineral substances, 30% of organic mass and 25% of water. A major part of the tooth mass is composed of dentin. The crown is composed of dentin and enamel, while cementum is found in the root surface. 95% of the enamel mass is represented by minerals. Dentin and cementum contain 70% and 60% of mineral substances (Lüllmann-Rauch, 2012).

Many studies have described the contents of elements in human bones (Katić et al., 1991; Smrčka, 2005; Zaichick et al., 2009; Zaichick and Zaichick, 2010a, b; Zaichick et al., 2011; Lanocha et al., 2012). Other studies have analyzed elements found in teeth (Curzon and Crocker, 1978; Curzon and Cutress, 1983; Vrbič et al., 1987; Lane and Peach, 1997; Reitznerová et al., 2000; Fischer et al., 2009, 2013; Ghadimi et al., 2013) or focused on elements in animal models (Yamaguchi et al., 1986; Arora et al., 2005; Hirayama et al., 2011; Oliveira et al., 2012; Maciejewska et al., 2014). Other publications describe the meaning of elements with respect to human bone metabolism (Sarko, 2005; Žofková, 2012; Dermience et al., 2015).

Smrčka (2005) studied distribution of elements in the femur and in the tibia of cadavers. He found, that the following elements were gathered in the epiphysis: Zn, V, Ni, Cr, Pb, Mn, Co, Sn, and in the central part of the diaphysis predominated: Ca, Sr, Na and K. This fact thus indicates a non-homogeneous distribution of elements in long bones. Based on the study of pre-historic skeletons the author also describes a change of the content of elements Zn, Sr and Pb in the pyramids of petrous bones and the proximal parts of femurs. The increase in concentrations of Zn, Sr and Pb in the pyramids of petrous bones and proximal parts of femurs in the curves related to age resembled the anthropometrically determined stages of growth acceleration. It was demonstrated on the level of inorganic elements seemed evident: 1) acceleration of growth between 0 and 2 years of age; 2) stabilisation of growth between 2 and 10 years of age; 3) acceleration of growth between 10 and 15 years of age; 4) stabilisation of growth between 15 and 20 years of age (Smrčka, 2005). In their study Katić et al. (1991) published different distribution of some chemical elements in human temporal bone. Lanocha et al. (2012) analysed the elements: Zn, Pb, Cu, Cd and Hg in the bones of the femur head obtained from patients after hip replacement surgery. The authors found out that Zn had the highest concentration and Hg the lowest. Zaichick et al. (2011) described effect of age and gender on 59 trace element in human rib. Reitznerová et al. (2000) described different distributions of elements in individual layers of the enamel. The Cu, Fe, Mn and Zn concentrations in four

layers of erupted and non-erupted teeth decreased while Mg and Sr concentrations increased toward enamel-dentine junction (Reitznerová et al., 2000). Lane and Peach (1997) described concentration of some elements in the human dental enamel depending on gender, age and geographical location. Fischer et al. (2013) described the change in the content of some elements in deciduous teeth depending on age. In their study Ghadimi et al. (2013) stated that the presence of trace elements in enamel could influence its physical properties. In their publication Curzon and Cutress (1983) were concerned with the link between trace elements and tooth disease. Maciejewska et al. (2014) determined the concentrations of Zn, Sr and Fe in rats (age: 7, 14 and 28 days) bone (mandible, skull, femur and tibia) and incisors. Zn and Sr concentrations were highest for the youngest individuals and decreased with age of rats, while Fe content was stable in bone matrix for most studied bones. The authors found higher Zn and Sr contents in the incisors compared to their contents in the mandible (Maciejewska et al., 2014). Oliveira et al. (2012) report a different Sr content in the bone and teeth of rats receiving strontium renalate. As reported by the authors, the incisor tooth presented high strontium incorporation levels, with strontium found in both the enamel and dentin along the whole extension of the tooth. The strontium content of the molar tooth was negligible. Distinct regions of the alveolar bone also seemed to present different strontium levels (Oliveira et al., 2012). Arora et al. (2005) determined in their study that high levels of Pb were observed in the superficial regions of enamel and in the dentine directly adjacent to the pulp. Hirayama et al. (2011) determined 29 elements in rat femurs aging from 5 to 113 weeks old. Yamaguchi et al. (1986) study indicates that, of the essential trace metals, zinc can effectively stimulate the bone growth and calcification with comparatively higher dose levels. This suggests a nutritional significance of Zn on bone growth. In their study Dermience et al. (2015) summed up the importance of 30 elements for bone metabolism. The constituent part of Žofková's publication (2012) is the significance of trace elements for bone metabolism.

Animal models are commonly used in the study of the inorganic component of bone tissue and teeth (Maciejewska et al., 2014). For example, as reported by Wang et al. (2001), the rat is appropriate for the study of osteoporosis in men as its bone remodelation is similar to that of humans. Bone strength is affected by the bone matrix volume and the microarchitectural distribution of this volume, and by the grade of mineralization. The grade of mineralization depends on the metabolic condition of the entire organism, not only on physical and chemical processes at the place of mineralization (Maciejewska et al., 2014). Various papers have focused on determining mandibular bone mineralization, for example, depending on its load (Tanaka et al., 2007; de Jong et al., 2013; Hichijo et al., 2015).

Hichijo et al. (2015) stated that the lower jaw showed a lower degree of mineralization in the ramus than in the corpus. In the soft-diet group, mineralization below the molars was increased compared to the hard diet group. Analysis showed inhibited growth of the ramus in the soft-diet group (Hichijo et al., 2015). The

higher mineral density in the corpus than in the ramus in rabbits was also stated in their study by de Jong et al. (2013). The difference of the mineralization in the mandible and at the same time importance of proper masticatory muscle function for craniofacial growth and development described Tanaka et al. (2007).

As reported by Zaichick and Zaichick (2010a), the knowledge of chemical elements contained in bones is essential to understand the aetiology and pathogenesis of bone diseases including osteoporosis. Mineral bone density of the mandible is important for osseointegration of dental implants and has an impact on the prognosis of periodontal disease (Buyukkaplan and Guldag, 2012). At the same time, reduced mineral bone density is associated with an increased risk of tooth loss (Krall et al., 1996). Trace elements in tooth enamel have been investigated for their role in caries and it was found that the presence of F, Al, Fe, Se and Sr is associated with a low risk of tooth caries, while Mn, Cu, and Cd have been associated with a high risk (Curzon and Crocker, 1978).

Experimental denervation

Studies focused on the effect of the nervous system on the bone have been done using various experimental models. Various methods can be used to make a sensory lesion, and causing a chemical lesion to the nerve is one of available options. In this respect, capsaicin has been commonly used (Hill et al., 1991; Adam et al., 2000; Offley et al., 2005; Apel et al., 2009; Ding et al., 2010; Kassab et al., 2013; Heffner et al., 2014). The transection of IAN is another option to achieve only a sensory lesion (Stewart, 1965; Retief and Dreyer, 1969; Torneck and Harnett, 1971; Hoffman and Tade, 1972). Hill et al. (1991) described reduced alveolar bone resorption after tooth extraction in animals receiving capsaicin since their birth. Similar results were reported by Adam et al. (2000). On the other hand, Offley et al. (2005) reported that capsaicin caused reduced levels of substance P and CGRP. Denervation using capsaicin leads to a loss of trabecular bone integrity, to reduction of bone mass and to a decrease in its strength. Additionally, it increases the number of osteoclasts, impairs osteoblast activity and new bone formation. Capsaicin causes a selective lesion to unmyelinated sensory neurons (Offley et al., 2005). In their study, Ding et al. (2010) described different results from those reported by Hill et al. (1991), Adam et al. (2000) and Offley et al. (2005).

A different capsaicin dose, different part of the studied bone and different animal age were considered as possible causes by Ding et al. (2010). As reported by the authors, sensory denervation caused by capsaicin increases bone resorption. As follows from the results, sensory innervation contributes to maintaining trabecular bone mass and mechanical properties through the inhibition of bone resorption (Ding et al., 2010). Apel et al. (2009) studied the effect of sensory denervation on the healing of a femoral fracture in the rat. These authors used locally applied capsaicin for sensory denervation. As shown by mechanical tests, sensory denervation of the bone decreased its resistance against load. The callus cross-

sectional area was larger for the denervated bone and its density was lower (Apel et al., 2009).

Kassab et al. (2013) published their method of causing a lesion to the IAN, achieving surgical exposure of the nerve using extraoral approach. The lesion was caused to the nerve by local application of capsaicin.

Surgical options for causing only a sensory lesion to a nerve are considerably limited because many peripheral nerves are of mixed nature and contain a motor component, as well. From this point of view, an experimental model with IAN lesion is appropriate. IAN is a sensory nerve that runs through the mandibular canal and contains no motor nerves (He et al., 2010). This nerve provides sensory innervation of mandibular bone and teeth (Nelson, 2015).

The use of experimental lesions to IAN is applied in the study of peripheral and central alterations caused by transection this nerve, by excising its part, by contusing or ligating the nerve. Experimental procedures used to obtain a lesion to IAN have been described by various authors (Stewart, 1965; Retief and Dreyer, 1969; Torneck and Harnett, 1971; Hoffman and Tade, 1972). When the IAN is injured, its distal part degenerates. This is associated with a change in the release of neuropeptides and in the bone metabolism. In this case, not only paresthesia occurs, but a mandibular bone integrity disorder also develops (Wu et al., 2016).

Hiroshima et al. (1998) focused on regenerating periodontal Ruffini ending of the rat incisor in connection with a resection to IAN. This similar problem was studied also by Harada et al. (2003). Yamashiro et al. (2000) described the effect of transection the nerve on bone remodelation during an experimental movement of the teeth. Lv et al. (2014) studied the healing of a periodontal defect and CGRP expression after IAN transection. No statistically significant difference was found in the volume of new bone formation by the authors. A difference was observed in bone mineralization, which was lower in the experimental group. Additionally, the study indicated that the nerve and the CGRP neuropeptide were important factors able to affect the quality of the regenerated alveolar bone through reduction of bone density during the mineralization process (Lv et al., 2014). The effect of causing a transection to the nerve on periodontal tissue regeneration was also studied by Yu et al. (2015). As reported by these authors, innervation influences OPG/RANKL (ostoprotegerin/receptor activator of nuclear factor kappa B ligand) ratio and neuropeptide expression, both of which responsible for periodontal alveolar bone regeneration processes (Yu et al., 2015). He et al. (2010) studied differences in the expression of substance P in the callus after mandibular osteotomy depending on IAN transection. As reported by these authors, low level of substance P was a result of IAN amputation and elevation of substance P may be caused by new nerve ingrowth into the bone callus. Substance P is involved in repairing and remodeling the mandible and that involvement of the IAN in the healing process of the mandible may by mediated by neuropeptides, such as substance P, which are released by the IAN (He et al., 2010). Ghassemi-Tary and Cua-Benward (1992) described the effect

of innervation on rat mandibular growth. Jacobsen and Heyeraas (1996) published the effect of capsaicin and of IAN transection on dentin formation in the first molar in the rat. As reported by these authors, capsaicin reduced CGRP and substance P-immunoreactive fibrils in the pulp. The transection of IAN resulted in an almost complete loss of immunoreactive fibrils in the pulp. Dentin formation was reduced in both groups compared to the control group (Jacobsen and Heyeraas, 1996).

Minimum information is found in the literature regarding the effect of sensory innervation on the inorganic bone and teeth component.

Conclusion

As follows from the literature, bone innervation is substantial for bone growth and remodelling. As indicated by the results of some studies, the distribution and contents of elements in long bones are different in the areas of the diaphysis and epiphysis. Less information is available regarding the distribution of these elements in the mandible. Distribution of chemical elements in the enamel has been described in greater detail. Innervation has an impact on pulp homeostasis. Different rates of mandibular bone mineralization have been described for the rat depending on the load of this bone. Bone mineralization is one of the factors that affect bone strength, healing of bone defects and fractures. It is important for osseointegration of dental implants and it also affects the prognosis of periodontal disease. Chemical elements have an impact on caries occurrence. Based on the literature, a certain effect of sensory innervation of the mandibular bone and teeth on the inorganic component can be assumed. This problem has not been deeply studied so far. IAN transection could be reflected in a change of the contents and distribution of chemical elements in the mandibular bone and teeth. It may be possible to interpret the results with respect to a similar condition in humans. Information learned in this manner could contribute to a better understanding of the effect of IAN on chemical elements in the mandibular bone and teeth. Future studies will focus on the research of effects exerted by IAN on the inorganic component of bones and teeth.

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 Prague Medical Report / Vol. 119 (2018) No. 4, p. 148–155

Comparison of Three Surgical Techniques in Pilonidal Sinus Surgery

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Received August 23, 2018; Accepted January 31, 2019.

Key words: Pilonidal sinus – Perforator flap – Rhomboid flap – Complication – Recurrence

Abstract: Our study aims to compare the surgical outcome of Limberg transposition flap, Karydakis flap, and primary closure after excision to treat sacrococcygeal pilonidal sinus disease. A total of 634 patients with pilonidal sinus who underwent surgery were evaluated retrospectively from January 2014 to January 2016. The patients were divided into three groups. Limberg transposition flap (LTF) was performed in 131 patients (group 1), Karydakis flap (KF) was performed in 232 patients (group 2) and primary closure (PC) after excision was performed in 271 patients (group 3). Patient demographics, operative and postoperative outcomes were recorded and analyzed retrospectively. The mean age ($p=0.98$), sex ratio ($p=0.74$) and removed sinus volume ($p=0.67$) were not statistically different between groups. Mean operative time was 54.3 ± 6.4 min for group 1, 46.8 ± 10.5 min for group 2, and 26.9 ± 5.8 min for group 3 respectively ($p=0.01$). When the length of hospital stay was compared, there was a significant difference in favor of primary closure ($p=0.01$). Regarding early surgical complication, Karydakis flap technique was superior to other groups ($p<0.001$). The recurrent rate was higher in the primary closure group ($p<0.001$). In our study, the primary closure method regarding the duration of surgery and hospitalization; Karydakis method regarding postoperative complications (seroma, hematoma, wound dissociation, infection, recurrence) were superior to the other two methods.

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https://doi.org/10.14712/23362936.2019.2

Introduction

Pilonidal sinus disease (PSD) is a chronic inflammation of the natal cleft and is mainly seen in young adults (Allen-Mersh, 1990; Hull and Wu, 2002). PSD usually occurs in healthy young men (male/female = 4–5/1). The incidence of the disease is approximately 26 per 100,000 people, with a mean age of 19 years for women and 21 years for men (Gurer et al., 2005). Although some earlier works have regarded the condition as congenital, it has recently become widely accepted that the condition is acquired (Bascom, 1983). Etiology of this disease is uncertain but relates to the implantation of loose hair into the depth of the natal cleft. Factors that affect the condition are the nature of hairs, the force of implantation and vulnerability of the skin (Shabbir et al., 2014). The goals in pilonidal sinus disease surgery are rapid healing, minimal hospital admission, minimal patient inconvenience, and low recurrence. There is no method satisfies all the requirements for the ideal treatment. The management of pilonidal disease depends on its presentation and ranges from simple incision and drainage to a wide excision with extensive reconstructive procedures (Varnalidis et al., 2014). Although many surgical procedures have been tried, the best surgical method remains controversial because of high recurrence rates. The recurrence rate after surgical treatment of PSD varies from 3 to 46% (Shafik, 1996).

There is no consensus on the optimal surgical management of the pilonidal sinus disease. Our objective is to compare the three methods used by our clinic and determine the outcomes retrospectively about operative time, hospitalization time, healing, postoperative complications, and recurrence.

Material and Methods

Between January 2014 and January 2016, 670 patients (Figure 1) underwent surgery for PSD in the Department of General Surgery at Siverek Government Hospital in Sanliurfa and Okan University Hospital in Istanbul. The data were collected after receiving permission from the hospital administration. A statement of informed consent was obtained from all patients before the operation. The patients who had previous PSD surgery (n=23) and concurrent abscess formation (n=13) were excluded from the study (Figure 1). The diagnosis of recurrent PSD was made based on clinical features. The remaining 634 patients who underwent surgery comprised the study groups and were evaluated retrospectively. All operations were performed by general surgery specialists with at least five years of experience. According to the types of surgeries that performed, patients were randomly divided into three groups. Patients who underwent Limberg transposition flap (LTF) were included in group 1, Karydakis flap (KF) were included in group 2 and excision, and primary closure (PC) were included in group 3, respectively. Patients with multiple sinus orifices in the sacrococcygeal region and the perianal region with a sinus opening less than 3 cm in length included in the KF group. Patients with more than three sinus orifice in the sacrococcygeal region and has sentinel sinus orifice 3 cm in the

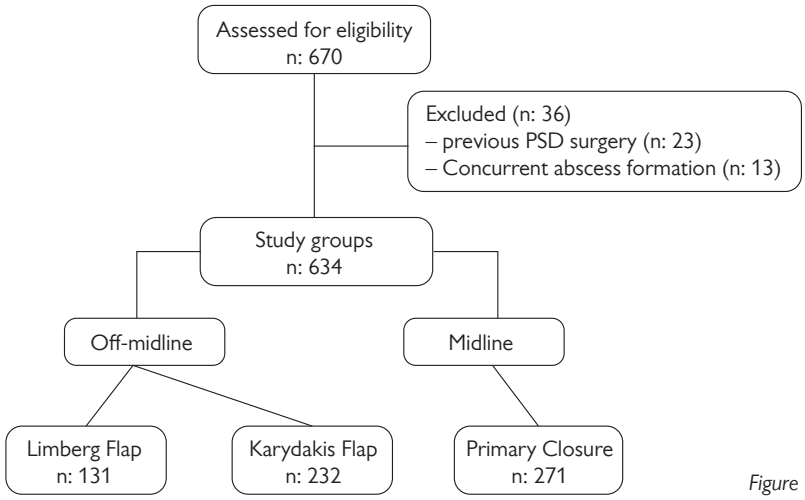

Figure 1 – Study groups.

distance from the sinus mouths included LTF group and patients with 3 or less sinus orifice in the sacrococcygeal region was preferred in PC group. In the study, age and gender of patients, type and duration of operation and length of hospitalization were evaluated. Postoperative early complications (seroma, hematoma, wound dehiscence, infection) and recurrence rates were compared between groups. The term "recurrence" is defined as fistula formation, wound dehiscence with abscess and purulent drainage from incision line in the first year after the operation.

Surgical technique

Hair of the gluteal and sacral regions was shaved before the operation. Preoperative bowel preparation was not used. In all cases, prophylactic antibiotics (cefazolin sodium at a dose of 1 g was given intravenously) were used at the time of induction of anesthesia. Patients were operated under Jack Knife position with spinal anesthesia. The gluteal skin was retracted toward to both sides using adhesive bandages to expose the intergluteal sulcus, and then methylene blue was administered in the sinus opening at the gluteal area. Excision of all sinus tracts, fistula borders, and scar tissues was carried out deep to the postsacral fascia and surrounding undamaged fibrolipomatous tissues. The volume of each piece removed was measured using a beaker and physiological saline. The volume of the overflowing physiological saline was taken as the total piece volume. Hemovac drain was used in patients with extracted sinus volume of 20 cc and above.

In LTF group, after removing the specimen, the Limberg fasciocutaneous flap was prepared by extending the incision down to and through the right or left gluteus maximus fascia (Varnalidis et al., 2014). The flap was sutured to the presacral fascia using 2/0 vicryl suture material. Subcutaneous tissues were approached

with 2/0 vicryl sutures. Skin closure was accomplished using 2/0 prolene mattress sutures.

In KF group, Karydakis flap extending along the incision was prepared with the medial edge of the wound being 1 cm deep and extending 2–3 cm medially (interiorly). The flap was displaced medially and sutured to the presacral fascia using 2/0 vicryl suture material. Subcutaneous tissues were approached with 2/0 vicryl sutures. Skin closure was accomplished using 2/0 prolene mattress sutures (Shafik, 1996).

In PC group, after removing the specimen, subcutaneous tissues were approached with no. 1 vicryl sutures. Skin closure was accomplished using 2/0 prolene mattress sutures.

All patients were released for mobilization on the first postoperative day. The suction drains were removed when daily drainage below 20 ml was obtained. In general, the patients were discharged on the first or second postoperative day for PC group and the third or fourth postoperative day for flap groups. The sutures were removed on the tenth postoperative day. The patients were advised to avoid pressure on the operated site for 10–15 days postoperatively. All cases were examined twice during the first two weeks, and once at the end of 1, 3, and six months after the operation, and yearly thereafter. The mean follow-up was 28 (22–35) months.

Statistical analyses were performed using SPSS (Statistical Package for the Social Sciences ver. 20.0, SPSS Inc., Chicago, Illinois, USA) computer software. One-way ANOVA test was used to compare the duration of hospital stay and operative time between the groups. Complications (seroma, hematoma, wound dehiscence, infection, recurrence) were analyzed using the chi-square test. Results were given as mean ± standard deviation. For all statistical analyses, $p<0.05$ was considered significant.

Results

A total of 634 patients (Figure 1) were included in the study (LTF: 131, KF: 232, PC: 271) and 36 patients were excluded due to previous PDS surgery (n=23) and

Table 1 – The demographic datas of the patients

Charecteristics	Limberg flap	Karydakis flap	Primary closure	P-value
Numbers (n)	131	232	271	
Gender (male/female)	25/106	42/190	58/213	0.740
Age (years)	26.31 ± 8.40	26.39 ± 7.34	26.44 ± 7.11	0.980
Hospitalization (days)	3.31 ± 0.87	2.10 ± 0.73	1.71 ± 1.48	0.001
Operating time (min)	54.31 ± 6.41	46.85 ± 10.46	26.94 ± 5.79	0.001
Specimen volume (cc)	28 ± 52	29 ± 51	28 ± 65	0.670

Values are mean ± standard deviation (range)

Table 2 – Postoperative outcomes and recurrence

Complications	Limberg flap	Karydakis flap	Primary closure	Total	P-value
Seroma (n/%)	13/9.92%	10/4.31%	41/15.13%	64/10.09%	<0.001
Wound dehiscence (n/%)	28/21.37%	19/8.19%	35/12.92%	82/12.93%	<0.002
Infection (n/%)	18/13.74%	12/5.17%	51/18.82%	81/12.78%	<0.001
Recurrence (n/%)	5/3.82%	5/2.16%	31/11.44%	41/6.47%	<0.001

concurrent abscess formation (n=13). There were 509 males and 125 females, and the average age was 26.39 ± 7.46. The demographic data of the patients are shown in Table 1. There was not any significant difference between groups regarding gender (p=0.74), age (p=0.98) and removed specimen volume (p=0.67). Days of hospitalization (p=0.001) and operative time (p=0.001) was shorter in midline closure group. The numbers of early postoperative complications (seroma, hematoma, wound separation, infection) and recurrences are summarized in Table 2. Recurrence rate (p<0.001), infection rate (p<0.001) and seroma rate (p<0.001) was higher in the midline group than flap groups. Wound dehiscence rate was higher in the LTF group (p<0.002).

Discussion

Management of pilonidal disease usually depends on the clinical presentation. While successful treatment has been achieved by shaving the hair on a regular basis, complex cases may require wide excision with extensive reconstructive procedures (Bailey et al., 2013; Spychala and Murawa, 2014). Surgery is usually preferred in the definitive treatment of pilonidal sinus disease. The mainstay of operative management for the chronic or persistent disease is excision of all pilonidal sinus tracts (Oncel et al., 2002; Petersen et al., 2002; Humphries and Duncan, 2010; Kepenekci, 2010). The optimal closure of the wound following an excision is debated. A close relationship has been reported between wound closure and postoperative morbidity and recurrence. Although many surgical techniques have been described for wound closure, most of these procedures fail to achieve the goals altogether. Primary closure can be accomplished by either midline or off-midline techniques including Z-plasty, V-Y advancement flap, Karydakis flap and Limberg flap (Bascom, 1987; Berkem et al., 2005).

It has been clearly stated in meta-analyses that off-midline closure should become standard management for pilonidal sinus when the closure is the desired surgical option (Omer et al., 2015). A systematic review and meta-analyses of randomized controlled trials including 1,573 patients showed benefits clearly with off-midline closure compared with midline closure (McCallum et al., 2008).

In our series, we compared midline closure with off-midline closure techniques including KF and LTF. The mean age was 26.4 ± 7, and 80.2% of the patients were male. Recurrence rate (11.4%), infection rate (18.8%) and seroma rate (15.1%) were higher in the midline group than flap groups ($p<0.001$). Only, hospitalization days (1.7 ± 1.5) and operative time (27 ± 6) were shorter in midline closure group. With the off-midline closure, the wound dehiscence incidence may be less developing due to less tension on the incision line, which may result in less recurrence than with midline closure. Also, because of the relatively high volume of specimens extracted in surgical flap techniques, drainage is used more often in these patients and therefore seroma may be less developing in off-midline closure techniques. In our study, it was observed that the specimen volumes obtained from off-midline closure patients were higher than those with midline closure, but there was no statistical difference between the two groups.

Karydakis (1992) reported a recurrence rate of 1%, a complication rate of 8%, and a length of hospital stay of 3 days. In our study, the recurrence rate was 2.2%, seroma rate 4.3%, infection rate 5.2%, wound dehiscence rate 8.2% and length of hospital stay of 2.1 ± 0.7 days in KF group. Our results are consistent with the literature in this study.

Successful results regarding LTF have been reported in the literature. In a study, low complication and recurrence rate and higher postoperative quality of life have been published with LTF (Omer et al., 2015). In another study, a lower recurrence and lower complication rate with LTF compared to KF has been reported (Arslan et al., 2014). On the other hand, some authors have stated a high complication rate in LTF. A study has reported 49% total complication rate with seroma 6%, wound dehiscence 45%, skin necrosis 10%, hematoma 6%, infection 4% and recurrent disease 13% (Käser et al., 2015). In the present study, the recurrence rate was 3.8%, seroma rate 9.9%, infection rate 13.7% and wound dehiscence rate 21.4% in LTF group. Wound dehiscence rate was higher (28 patients) in the LTF group. That may be due to surgical technique. Because the majority of wound dehiscence was not complete, and no major surgical intervention was required (the wound was sewn after cleaning) for these patients, but healing time was slightly longer.

Following surgical treatment of pilonidal disease, early postoperative morbidity and comfort is an important concern as well as recurrence. The most notable early postoperative problems are wound infection and wound dehiscence (Altintoprak et al., 2013; Bessa, 2013). In the present study, Karydakis flap group had 5.2% wound infection and 8.2% wound dehiscence while the LTF group had 13.7% wound infection and 21.4% wound separation. A significant difference was found between the groups ($p<0.001$).

There are also conservative or minimally invasive treatment options in PSD. Common conservative treatment is the administration of phenol to the sinuses. A study reported that the best treatment option for pilonidal sinus disease was crystallized phenol treatment with laser depilation (Girgin et al., 2012). In another

study, an innovative technique consisting in the destruction of the pilonidal cyst with a radial laser probe (FILACTM, Biolitec, Germany) has been described and concluded that the method could be proposed as a first-line treatment to the majority of patients with a pilonidal sinus disease (Dessily et al., 2017). In our opinion, the anatomic problem (narrow and deep natal cleft) which is an etiological factor in the development of PSD remains untreated in these techniques, and also recurrences rate is still high.

Conclusion

In this retrospective study, where we compare three widely used surgical methods in recent times, a significant difference was found between the techniques regarding early postoperative complications and recurrence risk. We believe that both off-midline closure methods can be safely used in PSD treatment, while KF group provides better results than LTF group regarding early postoperative complications. Midline closure method was superior regarding duration of surgery and hospitalization but has no advantage regarding early complications and recurrence.

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 Prague Medical Report / Vol. 119 (2018) No. 4, p. 156–164

The Age Dependent Progression of Hajdu-Cheney Syndrome in Two Families

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Received November 28, 2018; Accepted January 31, 2019.

Key words: Hajdu-Cheney syndrome – Short stature – Wormian bones – Acro-osteolysis

Abstract: Hajdu-Cheney syndrome (HCS) is a rare multi-system disease with autosomal dominant inheritance and skeletal involvement, resulting mostly in craniofacial dysmorphy with mid-face hypoplasia, dental anomalies, short stature, scoliosis, shortening of the digits and nail beds, acro-osteolysis and osteoporosis. We report the progression of clinical and radiographic findings in five patients with Hajdu-Cheney syndrome from two families. A custom capture array designed to capture exons and adjacent intron sequences of 230 selected genes were used for molecular analyses, and the pathogenic variants identified were confirmed by PCR and Sanger sequencing. In both families we observed age-dependent changes in the disease, with a progression of pain in older patients, a shortening of digits and nail

This study was supported by projects of the Ministry of Health (RVO-VFN 64165/2012) and the Ministry of Education, Youth, and Sports of the Czech Republic (PROGRES Q32/LF2).

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https://doi.org/10.14712/23362936.2019.3

beds on both the hands and feet, kyphoscoliosis and the persistence of Wormian bones in lambdoid sutures. Molecular analyses performed in two patients revealed that they are heterozygotes for a c.6255T>A (p.Cys2085*) variant in the *NOTCH2* gene, resulting in a premature stop-codon. Bone mineral density (Z-score < –2) did not improved in a girl treated with calcium and vitamin D supplementation during childhood and bisphosphonate during adolescence. Hajdu-Cheney syndrome is a slowly progressive disease with a frequently unfavourable prognosis in elderly patients, especially for the development of dental anomalies, osteoporosis and the progression of skeletal complications requiring orthopedic surgeries.

Introduction

Hajdu-Cheney syndrome (HCS) is a rare multi-system disease with skeletal involvement and autosomal dominant inheritance, and is associated with mutations in the terminal exon 34 of the *NOTCH2* gene encoding the transmembrane NOTCH2 receptor (Isidor et al., 2011; Simpson et al., 2011; Adami et al., 2016; Pittaway et al., 2018). The disease is slowly progressive with an onset in childhood or adolescence resulting in short stature, craniofacial dysmorphism with mid-face hypoplasia, hypertelorism, bushy eyebrows, micrognathia, small mouth and dental anomalies, vertebral anomalies, scoliosis, and bowing of the long bones. Multiple Wormian bones in scull sutures and acro-osteolysis of the distal phalanges on X-ray and osteoporosis are typical findings. Other features may develop, including hearing loss, renal cysts and cardiovascular involvement (Ramos et al., 1998; Isidor et al., 2011; Regev et al., 2019).

Here we present the age-dependent progression of clinical and radiological manifestations of Hajdu-Cheney syndrome in five patients from two families.

Methods

DNA was isolated from peripheral blood. For molecular genetic diagnostics of skin, bone, and connective tissue disorders, we developed a solution-based capture method using the SeqCap EZ Choice Library (Roche NimbleGen, Madison, WI, USA) and targeted sequencing on a NextSeq (Illumina, San Diego, CA, USA). Sequencing data were evaluated using the software Sequence Pilot (JSI Medical Systems, Kippenheim, Germany). A custom capture array was designed to capture exons and adjacent intron sequences of 230 selected genes, among them the gene *NOTCH2* associated with Hajdu-Cheney syndrome. Identified pathogenic variants were confirmed by PCR and Sanger sequencing using the BigDye Terminator Cycle Sequencing Kit (Applied Biosystems Foster City, CA, USA) on an ABI 3130xl Genetic Analyzer (Applied Biosystems).

Ethics

The study was approved by the Ethics Committee of the General University Hospital in Prague and was conducted in agreement with the Declaration of Helsinki. Written

informed consent for molecular analyses was obtained from a 19-year-old girl and a 17-year-old boy and his mother.

Patients

The proband (P1) from the first family is a 17-year-old boy with a behavioural disturbance, ADHD (attention deficit hyperactivity disorder) and border low mental capacity (IQ 76–80), short stature (167 cm, 3rd percentile), mid-face hypoplasia with bushy eyebrows, synophrys, down-slanted palpebral fissures, micrognathia, a mixed set of teeth with the persistence of one milk tooth and the delayed eruption of two teeth, hypermobility of large joints, kyphoscoliosis, bowed legs, dyskeratosis, and a mild shortening of several nail beds since infancy (Figure 1). During early childhood he had frequent upper respiratory infections and recurrent warts on his palms and soles regardless of therapy that including surgery and liquid nitrogen. His growth percentile gradually declined from the 40th percentile at birth to the 10th percentile at the age of 10 years and the 3rd percentile after puberty. The bone mineral density

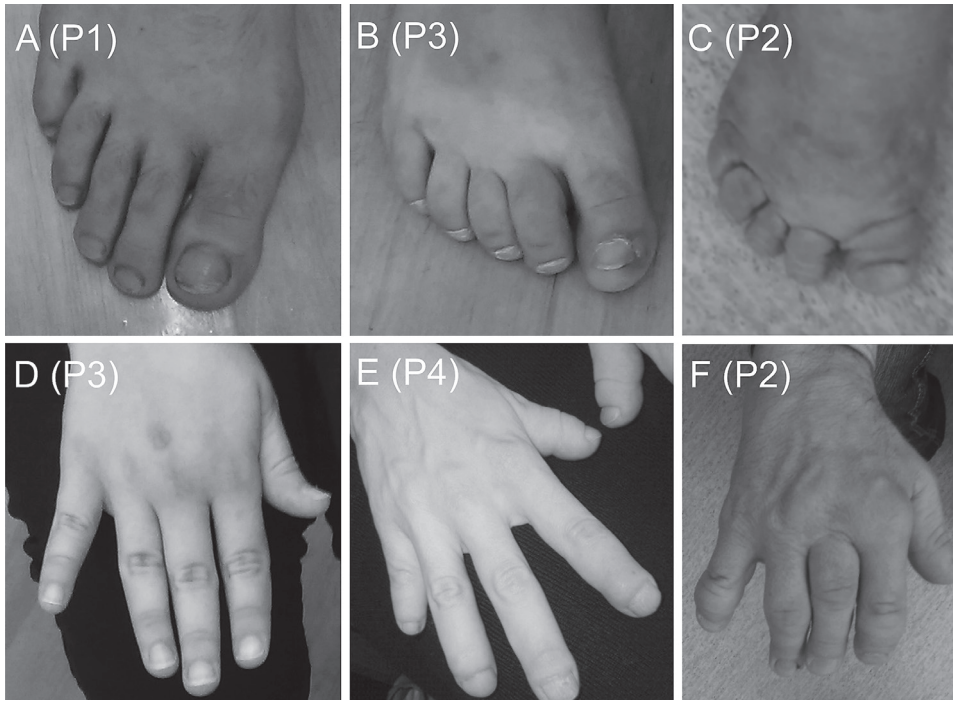

Figure 1 – Photographs of feet (above) and hands (below) in patients with Hajdu-Cheney syndrome: (A) mild shortening of the nail beds on the foot of a 17-year-old boy (P1); (B) shortening of several nails in his 19-year-old sister (P3); (C) very short digits and nails in their 55-year-old father (P2); (D) nearly normal digits on the hand of the 19-year-old girl (P3); (E) very short digits and nails in her father (P2); (F) shortening of digits I and V in a 24-year-old women (P4).

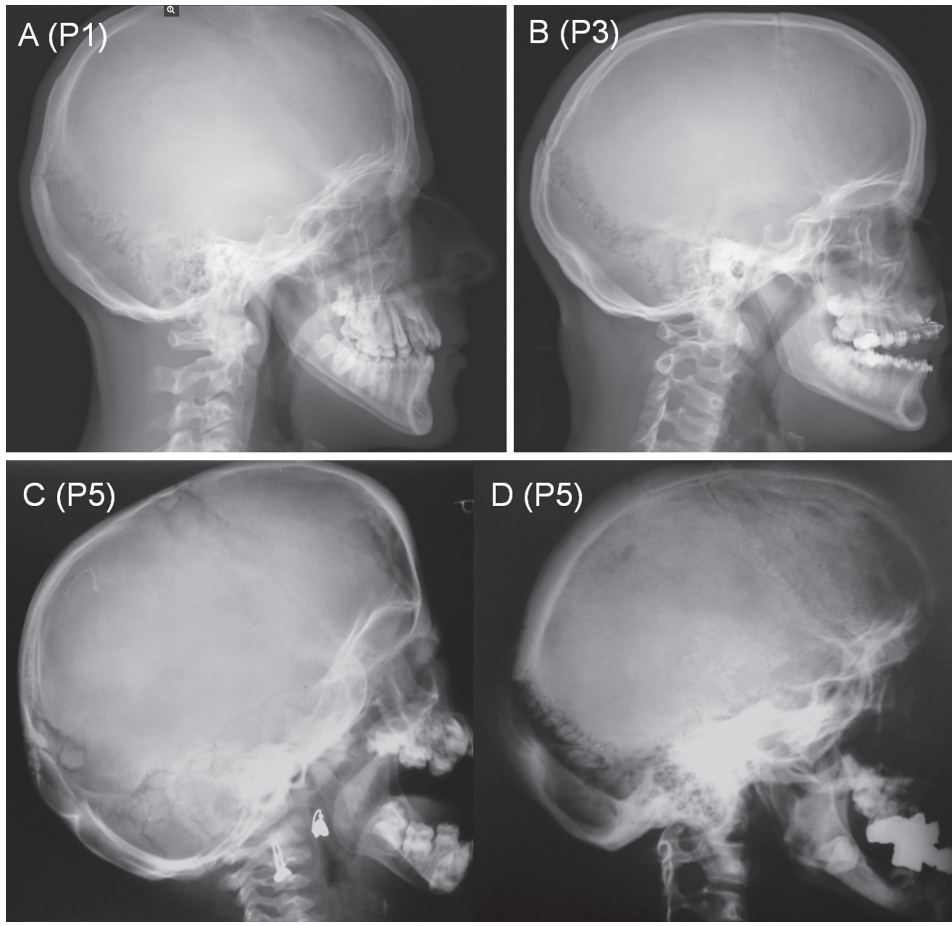

Figure 2 – Wormian bones in the lambdoid sutures, dental abnormalities and hypoplasia of frontal cavities in patients with Hajdu-Cheney syndrome: (A) a 17-year-old boy (P1); (B) a 19-year-old girl (P3) and progression of the disease in the girl (P5) from the age of 3.5 years (C) to the age of 15 years (D).

(BMD) of the lumbar spine is decreased (Z-score –1.6). An X-ray survey revealed multiple Wormian bones in the lambdoid suture, dental abnormalities, hypoplasia of the frontal sinuses (Figure 2) and acro-osteolysis on toes I–III and all fingers (Figure 3).

His father (P2) is a 55-year-old man with short stature (165 cm, < 3rd percentile) and sore fingers on both hands and feet since the second decade of his life, progressively resulting in acquired deformities and a profound shortening of most of the fingers and the loss of several nails (Figure 1). He has repeatedly been seen by several specialists and treated with antibiotics and anti-inflammatory drugs without any success. He has increasing problems with sore joints on the hands and feet, has

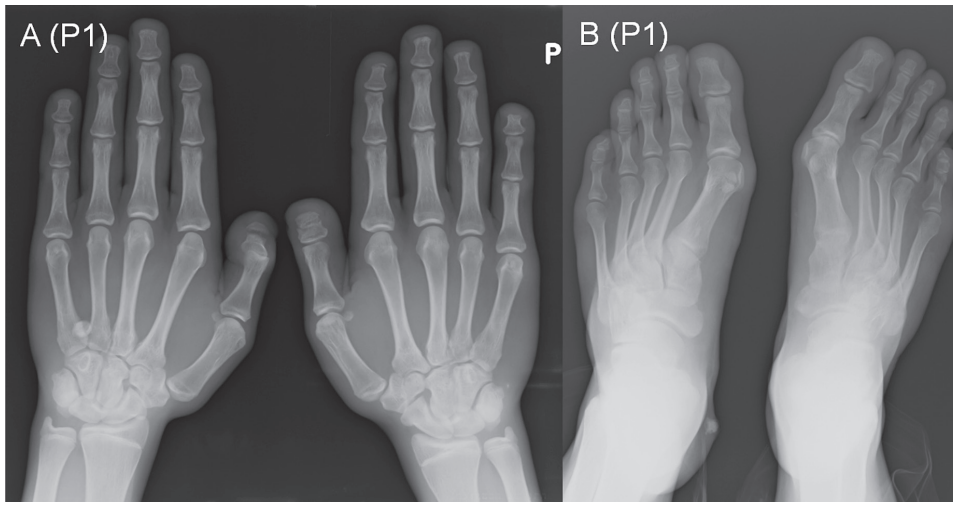

Figure 3 – Acro-osteolysis of all distal phalanges on the hands (A) and distal phalanges I–III on the feet (B) of a 17-year-old boy with Hajdu-Cheney syndrome (P1).

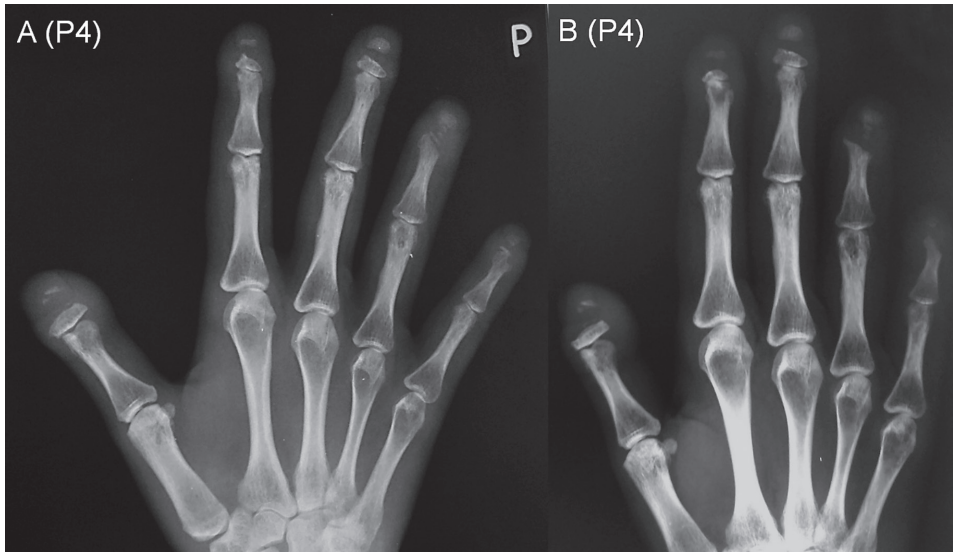

Figure 4 – Progression of acro-osteolysis in patient with Hajdu-Cheney syndrome (P4) from the age of 24 years (A) to the age of 40 years (B).

flat feet, and he is unable to walk longer distances. The soft tissue and skin on several fingers are frilled. He has normal dentition and wears glasses for hyperopia.

The proband's sister (P3) is a 19-year-old girl with low stature (155 cm, 3rd percentile). She has severe myopia (contact lenses –7 D), mild mid-face hypoplasia

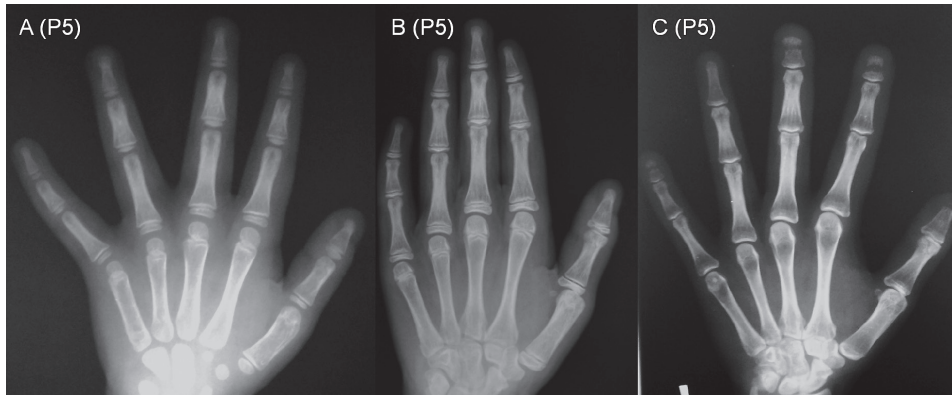

Figure 5 – Progression of acro-osteolysis in patient with Hajdu-Cheney syndrome (P5) at the age of 8 (A), 14 (B) and 16 (C) years.

and fixed braces after surgery of the upper jaw. Further abnormities include genua valga, flat feet, and several short nails on her feet (Figure 1). An X-ray revealed multiple Wormian bones in the lambdoid suture, dental abnormalities and hypoplasia of the frontal sinuses (Figure 2).

The second family was partly reported in 1994 (Zeman et al., 1994). At the age of 24 years the proband (P4) had progressive back pain, short stature, mid-face hypoplasia, dental anomalies, shortening of several digits (Figure 1) with acro-osteolysis on both hands and Wormian bones in the lambdoid suture. She required several spine surgeries because of severe kyphoscoliosis, used a wheel-chair since the end of her fourth decade, and died at the age of 43 years.

Her daughter (P5) had hypertelorism and normal X-rays of her hands at the age of 2.5 years, but her first acro-osteolysis appeared a year later. In addition, Wormian bones in the lambdoid sutures were observed at the age of 3.5 years. Since the age of 13 years, she has had acro-osteolysis on most fingers of both hands (Figure 5). She has also developed kyphoscoliosis and underwent neurosurgery because of progressive headaches due to a Chiari II malformation with basilar impression at the age of 14 years, and surgery for dentition abnormalities one year later. Currently she has short stature (148 cm, < 3rd percentile), and the BMD of her lumbar spine and femoral neck has repeatedly been in the range indicating osteoporosis (Z-score < –2) despite therapy with bisphosphonates, calcium and vitamin D supplementation.

Results

The results of molecular analyses demonstrated that patients P1 and P2 are heterozygotes for the novel c.6255T>A (p.Cys2085*) variant in the *NOTCH2* gene resulting in a premature stop-codon. The mutation is not described in the databases HGMD® Professional 2018.4 and ClinVar. DNA from the members of the second family (P4, P5) is not available.

The disease progression with the age-dependent shortening of digits and nails on the feet in patients P1–3 and the hands in patients P2–4 are shown on Figure 1. Radiographic findings in patients P1 and P3 revealed skull abnormalities with Wormian bones in the lambdoid sutures, dental abnormalities and hypoplasia of the frontal sinuses (Figure 2A and B). The progression of skull abnormalities in P5 during childhood is shown in Figure 2C and D. Acro-osteolysis of all distal phalanges on the hands and three distal phalanges on the feet of P1 at the age of 17 years are shown on Figure 3. Figures 4 and 5 document the development of acro-osteolysis in P4 between the age of 24 and 40 years, and P5 during her childhood and adolescence, respectively.

Discussion

A new type of cranio-skeletal dysplasia was described in 1948 by Hajdu and Kauntze, and since 1965 has been reported as Hajdu-Cheney syndrome (Hajdu and Kauntze, 1948; Cheney, 1965). The disease is caused by the mutation in exon 34 of the *NOTCH2* gene, encoding the transmembrane NOTCH2 receptor involved in the coupled processes of bone formation and resorption (Pittaway et al., 2018). This *NOTCH2* mutation leads to the premature truncation of the transmembrane NOTCH2 receptor, with either the disruption or loss of the C-terminal proline-glutamate-serine-threonine-rich proteolytic recognition sequence with enhanced NOTCH2 signaling activity (Simpson et al., 2011; Canalis and Zanotti, 2014). In a mouse model of Hajdu-Cheney syndrome with the mutation 6955C>T in *NOTCH2* resulting in a Q2319X change at the amino acid level, bone osteopenia, enhanced osteoclastogenesis and increased bone resorption were found (Canalis et al., 2016).

Diagnosis of Hajdu-Cheney syndrome is based on clinical suspicion in combination with the results of X-ray survey and molecular analyses. Although multiple Wormian bones and acro-osteolysis are quite typical for patients with Hajdu-Cheney syndrome, they are not sensitive enough for the diagnostics, because acro-osteolysis may clinically manifest only with minimal nails or skin changes and the radiographic findings of Wormian bones and acro-osteolysis may also occur in patients with other inherited or acquired diseases. For example, multiple Wormian bones are common in infants with osteogenesis imperfecta and acro-osteolysis may be found in patients with pycnodysostosis, severe psoriasis, systemic sclerosis, Raynaud's disease or other chronic vascular disturbances. The age of patients with Hajdu-Cheney syndrome at the onset of the first acro-osteolysis, which was documented by the X-ray, is variable, from one year (Gong et al., 2017) to the second or third decade. Acro-osteolysis in our youngest patient (P5) was documented at the age of 3.5 years, while patient P3 still has no acro-osteolysis in her adolescence. Renal abnormalities, especially the polycystic kidney disease may be found approximately in 10% of patients with Hajdu-Cheney syndrome, but end-stage renal disease is rare (Battelino et al., 2016). So far, the renal functions in our patients P1 and P2 are normal.

The prognosis of patients with Hajdu-Cheney syndrome is unfavorable and therapy is symptomatic, especially after the development of dental and orthopedic complications. The response to bisphosphonate treatment in preventing and/or treating already existent osteoporosis is variable and age-related, but probably less effective with advancing age (Galli-Tsinopoulou et al., 2012; Adami et al., 2016; Pittaway et al., 2018). Therapy with denosumab may increase bone mineral density, but does not prevent the progression of acro-osteolysis (Adami et al., 2016). The Z-score of bone mineral density did not improve in our patient (P5) treated with calcium and vitamin D supplementation during childhood and bisphosphonate during adolescence.

Conclusion

Hajdu-Cheney syndrome is a slowly progressive disease with usually an unfavorable prognosis in the elderly, mainly due to the development of dental anomalies, osteoporosis, and the progression of severe skeletal complications requiring orthopedic surgeries.

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Long-term Survival of Patient with Ampulla of Vater Metastasis of Renal Cell Carcinoma

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Received October 1, 2018; Accepted January 31, 2019.

Key words: Renal cell carcinoma – Metastasis – Ampulla of Vater – Pancreatoduodenectomy

Abstract: Ampulla of Vater metastases from renal cell carcinoma are rare. The time between detection of the primary tumour and its metastasis may extend to years. Management should be aggressive, since the prognosis of renal cell carcinoma is unpredictable and curative surgery of metastases may extend patient survival and even lead to definite cure. Herein we report a case of long-term survival after successful surgical treatment of a renal cell carcinoma metastasis to the ampulla of Vater. A 62-year-old man with a history of renal cell carcinoma in the left kidney underwent a successful left nephrectomy. Eight months later duodenoscopy showed a tumour at the site of papilla of Vater. Biopsy confirmed the diagnosis of carcinoma. Contrast enhanced computer tomography scan verified the periampullary mass, dilatation of the pancreatic and the common bile duct. No radiological signs of either local advancement or distant metastases were present. Pylorus-preserving pancreatoduodenectomy with lymphadenectomy was performed. Pathology report disclosed metastatic lesions in the papilla of Vater from the clear cell carcinoma of the kidney. The postoperative course was uneventful, and the patient lived for 14 years after pancreatoduodenectomy and, following thorough investigations, was free from local and systemic recurrence. Pancreatoduodenectomy can provide long-term survival in selected cases with solitary papilla of Vater metastasis from renal cell carcinoma. Favourable long-term survival rates suggest that these patients should be considered candidates for pancreatoduodenectomy if experienced pancreatic surgeon is available and no other metastases are found.

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https://doi.org/10.14712/23362936.2019.4

Introduction

Renal cell carcinoma is a neoplasm with unpredictable course even after metastasing (Pavlakis et al., 2004). Metastases from this type of cancer have been described from various organs, but ampulla of Vater metastases seem to be extremely rare, as only 12 cases have been reported in the literature. Even though there are several case reports of metastases to nearby pancreas (Hirota et al., 1996; Hashimoto et al., 2001; Wente et al., 2005; Karakatsanis et al., 2013; Haidong et al., 2014), and a case report of metastases both to the duodenum and the pancreas (Hashimoto et al., 2001), there are no obvious explanations for metastasis potential discrepancy in these sites.

Early stages of tumours metastasing to the ampulla of Vater usually give rise to few symptoms and signs, which make diagnosis difficult. Despite that, aggressive surgical treatment has been advocated for all solitary metastases arising from renal cell carcinoma, including ampullary metastases (Wente et al., 2005; Haidong et al., 2014). Discussing treatment options, it is important to bear in mind that patients with one metastasis may also have occult tumours in other sites (Merino et al., 2005). In this case report, we describe a patient with ampullary metastasis from renal cell carcinoma, presenting with abdominal pain. The diagnosis was established by means of endoscopy and biopsy and the patient has undergone successful surgery.

Case report

A 62-year-old man with a history of renal cell carcinoma in the left kidney underwent a successful left nephrectomy. Eight months later the patient was admitted to the Hospital of Lithuanian University of Health Sciences (Kaunas, Lithuania) with severe upper abdominal pain, jaundice, general weakness and subclinical signs of gastric outlet obstruction. Serum analysis revealed slight increase in total and direct bilirubin (64.8 μmol/l and 42.5 μmol/l respectively), whereas serum amylase was normal. Abdominal pain and jaundice have been described as transient during the course of his disease. Laboratory results were unspecific whereas duodenoscopy showed a tumour at the site of papilla of Vater. Biopsy confirmed the diagnosis of carcinoma. Contrast enhanced CT (computed tomography) scan verified the periampullary mass, slight dilatation of the pancreatic and the common bile duct. No radiological signs of either local advancement or distant metastases were present.

Standard pylorus-preserving pancreatoduodenectomy with regional lymphadenectomy was performed as no other manifestation of the malignancy was found. The underlying vascular structures were not involved by the tumour and the resection was classified as curative. Gross examination of the specimen revealed two tumours in the duodenum, one of them involving papilla of Vater and obstructing the orifice. Final pathology report disclosed the metastatic lesions in the duodenum and the papilla of Vater from the clear cell carcinoma of the kidney (Figure 1), also confirmed by immunohistochemical staining (Figure 2). Twenty lymph nodes in the surgical specimen were negative for metastatic lesions and the resection margins

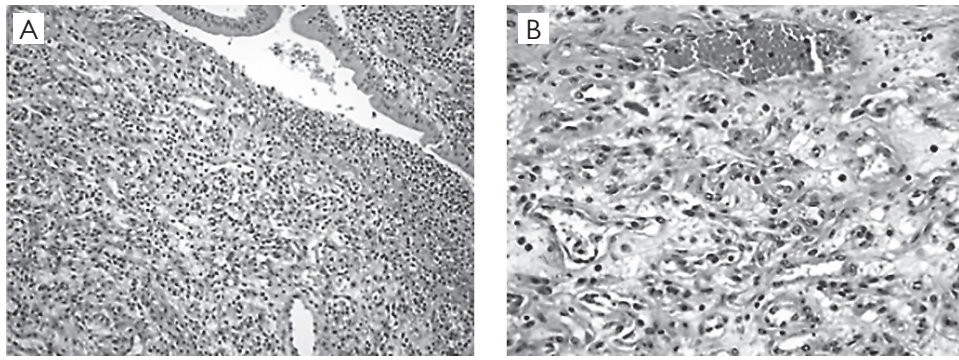

Figure 1 – Microscopic examination of the resected duodenum and pancreas.
Microscopic examination of the resected duodenum and pancreas show clear cell carcinoma compatible with metastasis from renal cell carcinoma. Tumour cells are large, with abundant eosinophilic cytoplasm. Their appearance is highly suggestive of renal cell carcinoma cells (hematoxylin-eosin, a: ×200, b: ×400).

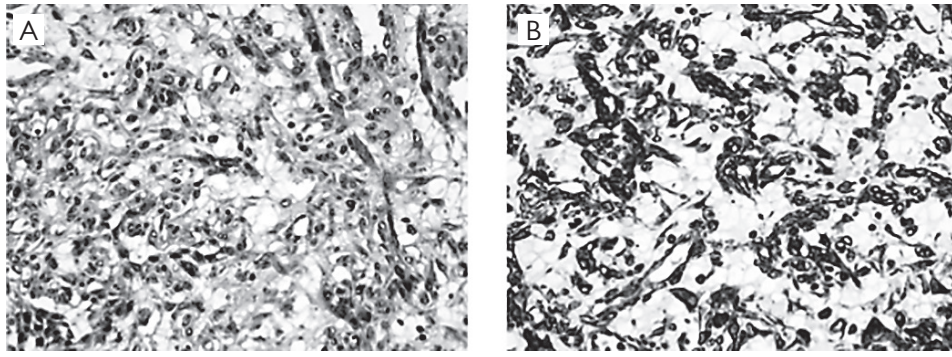

Figure 2 – Histological section of the ampullary wall.
The diagnosis renal cell carcinoma metastasis is confirmed by the immunohistochemical detection of cytokeratin (a) and vimentin (b).

were free. The postoperative course was uneventful, and there were no signs of local and systemic recurrence. Patient died from cardiovascular disease 14 years.

Discussion

Distant metastases are dominating the course of renal cell carcinoma in more than 60% of patients (Pavlakis et al., 2004; Wente et al., 2005). Renal cell carcinoma may spread to any organ, the most common sites for metastases being the lymph nodes, lung, bone, skin, adrenal glands, liver, opposite kidney, brain (Jacobs et al., 2013) and – to a smaller extent – pancreas (Hirota et al., 1996; Hashimoto et al., 2001; Wente et al., 2005), whereas ampullary metastases are reported to be extremely rare (Pavlakis et al., 2004; Merino et al., 2005; Ogiso et al., 2005; Zhao

et al., 2012; Smigielski et al., 2013). To our knowledge, there are only 12 cases of ampulla of Vater metastases from renal cell carcinoma reported in the English, German, Japanese, and Scandinavian literature (Leslie et al., 1996; Janzen et al., 1998; Merino et al., 2005; Ogiso et al., 2005; Chowdhury et al., 2014; Cheong et al., 2018; Sarocchi et al., 2018).

Le Borgne et al. (2000) provided a detailed analysis of symptoms and signs of metastatic tumours of the ampullary region. The most common symptoms of presentation were jaundice, acute pancreatitis related to pancreatic duct obstruction, and upper gastrointestinal tract bleeding. In the majority of patients, it is not possible to differentiate clinically metastatic lesions in the papilla from a primary tumour, although this would obviously be of importance in patients with a history of malignancy.

It is of certain interest to find that the mean time interval between surgery for a primary tumour and the diagnosis of a metastatic ampullary tumour was 88 months in the study of Le Borgne et al. (2000). Regarding the prognosis, the longer the interval between the primary tumour resection and the diagnosis of metastases the longer the disease-specific survival may be expected (Hirota et al., 1996; van der Poel et al., 1999). The efficacy of operative resection of localized renal carcinoma metastatic lesions in the liver, lungs, and brain is well established and an aggressive approach is suggested (Nakeeb et al., 1995; Leslie et al., 1996; Le Borgne et al., 2000). A series from The Johns Hopkins' has also shown favourable results regarding survival rate of the patients, operated on because of primary periampullary carcinoma followed by radically intended metastasectomy (Nakeeb et al., 1995). Curative pancreatectomy resulted in zero mortality and an overall survival of 35% at 2 years and 17% at 5 years according to Le Borgne et al. (2000) report. This means that surgery is indicated not only as a life-saving procedure to manage metastasis-related complications, e.g. intestinal obstruction, gastrointestinal bleeding, and jaundice, but also as an elective procedure with the aim to resect the metastatic lesion with the aim of cure (Haidong et al., 2014). However, the majority of patients with renal cell carcinoma metastases eventually require complementary systemic therapy, because they often already have metastases in other locations – not seldom occult until carefully looked for. Therefore, treatment in such cases must be individually tailored.

In conclusion, we report a case of ampulla of Vater metastasis from renal cell carcinoma. Severe transient epigastric pain, possibly due to outflow obstruction of the pancreatic duct, and transient jaundice were the major manifestation of the metastasis. The patient was successfully treated by curative pancreatoduodenectomy. In the absence of generalized metastatic disease, it is obvious that pancreatoduodenectomy can provide long-term survival in selected cases with solitary metastasis. Favourable long-term survival rates suggest that these patients should be considered candidates for pancreatoduodenectomy as long as experienced pancreatic surgeon is available and no other metastases are found.

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 Prague Medical Report / Vol. 119 (2018) No. 4, p. 170–173

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ISSN 1214–6994

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Prague Medical REPORT

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Published by the First Faculty of Medicine, Charles University, Karolinum Press,
Ovocný trh 560/5, 116 36 Praha 1 – Staré Město, Czech Republic, www.karolinum.cz

Editorial Office: Prague Medical Report, Kateřinská 32, 121 08 Prague 2, Czech Republic,
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Published as quarterly journal. Typeset and printed by Karolinum Press.
Annual subscription (4 issues) EUR 60,–. Single copy EUR 20,–.
Distribution: Karolinum Press, Ovocný trh 560/5,
116 36 Praha 1, Czech Republic, e-mail: journals@karolinum.cz

ISSN 1214-6994 (Print)
ISSN 2336-2936 (Online)

Reg. No. MK ČR E 796