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Recent Advances in Diagnosis and Severity Assessment of Acute Pancreatitis

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Key words: Acute pancreatitis – Diagnostic criteria – Diagnostic algorithm – Classification – Severity assessment – Recent advances – Scoring system

Abstract: The incidence and prevalence of acute pancreatitis (AP) is increasing over time. The diagnosis of acute pancreatitis is established by revised Atlanta criteria (2012). Multiple criteria and scoring systems have been used for assessment of severity of AP. Majority of acute pancreatitis cases (80%) are mild, the challenge remains in early diagnosis, severity assessment and treatment of severe AP and its complications. Assessment of severity of AP is important part of management because line of treatment depends on aetiology and severity of acute pancreatitis. In this article a comprehensive review of recent advances in diagnosis and severity assessment of acute pancreatitis has been described.

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Introduction

Course of acute pancreatitis (AP) is highly heterogeneous and at risk for development of persistent organ failure early in the course of severe AP. The incidence of acute pancreatitis is increasing worldwide, and it is one of the common gastrointestinal causes of hospital admission. The incidence of AP in USA, Scotland and Finland are 49.3, 41.9 and 46.6 per 100,000 populations, respectively (Toouli et al., 2002). In Europe and other developed nations like Hong Kong, more patients tend to have gallstone pancreatitis, whereas alcoholic pancreatitis is most common in United States. Alcohol and gallstones were the most common causes of acute pancreatitis in India (Mukherjee et al., 2017; Sharma et al., 2017; Negi et al., 2018). It is possible to identify the aetiology of AP in around 80% of cases and 20% is classified as idiopathic AP (Working Party of the British Society of Gastroenterology et al., 2005). Most patients with AP recover spontaneously with supportive measures in a short period of time but it has life-threatening potential in minority cases (Phillip et al., 2014). Over 80% of patients have mild, self-limiting AP and severe pancreatitis occurs in less than 20% of AP patients, characterized by a protracted clinical course, multiorgan failure, and pancreatic necrosis (Whitcomb, 2006). The mortality in severe acute pancreatitis is as high as 30% (Whitcomb, 2006), but the overall mortality in AP is 5% (NICE, 2016). It is important to identify AP patients who are at risk for development of persistent organ failure early in the course of the disease (Otsuki et al., 2013). To decrease the mortality rate of the severe acute pancreatitis, it is important to evaluate the severity of AP early in the disease course and initiate appropriate treatment according to severity and aetiology (Juneja et al., 2010). Only clinical signs and symptoms are not reliable for severity assessment in majority of cases and they should be supported by objective measures (Takeda et al., 2010). Several scoring systems are useful for assessing the severity of AP and for deciding the treatment strategy and the need for transfer to a specialist unit (Takeda et al., 2010).

Diagnosis

The diagnostic probability of acute pancreatitis is based on the index of suspicion of clinician, which is largely based on the patient's history and examination findings (Figure 1). Revised Atlanta classification (2012) is used for diagnosis of acute pancreatitis which requires at least 2 of the following three criteria: 1) abdominal pain consistent with that of AP, 2) biochemical evidence of acute pancreatitis (serum amylase or lipase elevation >3 times the upper limit of normal), and 3) characteristics findings of AP seen in cross-sectional abdominal imaging (Banks et al., 2013).

Character of abdominal pain in acute pancreatitis

Abdominal pain consistent of acute pancreatitis means moderate to severe epigastric pain which is radiating to the back (seen in 40–70% of patients) and lasting for several hours to days (Tenner et al., 2013; Greenberg et al., 2016). Abdominal pain is the

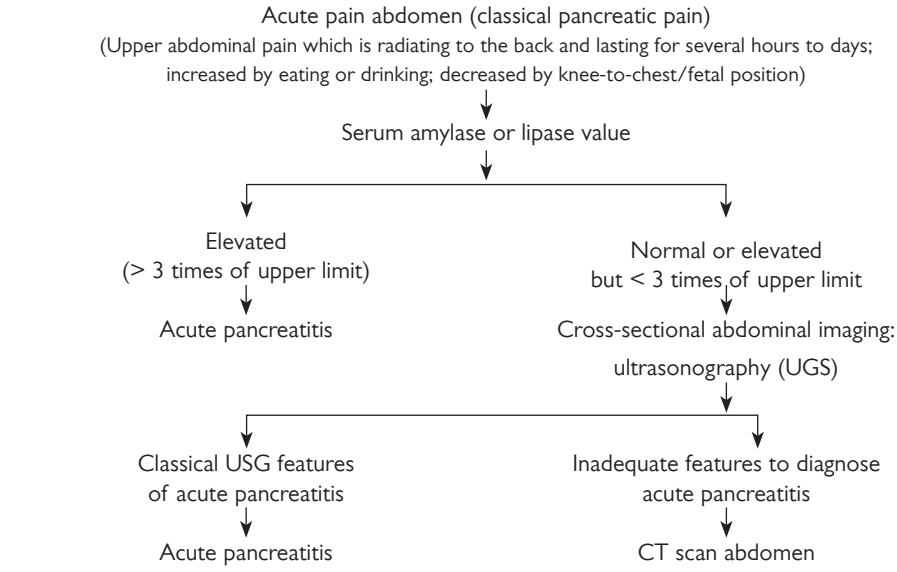

Figure 1 – Diagnostic algorithm of acute pancreatitis.

cardinal symptom which occurs in about 95% of cases of AP. Typically pain involves the upper abdomen or more localized to epigastric area, or left upper quadrant. It is acute pain without prodromal symptoms which reaches maximum intensity within minutes to hours and tends to be moderately to intensely severe. The pain tends to be steady but intensity is increased by eating or drinking (especially alcohol). Knee-to-chest (fetal position) position decreases the pain intensity by decreasing the stretch of the pancreas. Due to retroperitoneal location of pancreas, pain is typically boring and deep in nature. It often radiates in to the lower thoracic region of the back. About 90% of patients of AP have nausea and vomiting due to peripancreatic inflammation involving posterior gastric wall which leads to gastroparesis and causing localized or generalized ileus (Cappell, 2008).

Physical signs of acute pancreatitis

Mild pancreatitis patients usually present with little abdominal tenderness on palpation but severe pancreatitis may present with severe abdominal tenderness on palpation, guarding generally localized to the upper abdomen and absence of bowel sounds due to paralytic ileus (Tenner et al., 2013; Greenberg et al., 2016). An around 60% patient with AP in early course develops low-grade fever due to peripancreatic inflammation but does not have evidence of infection. Cullen's and Turner signs are seen in about 3% of AP patients and are associated with high mortality (~ 37%). These signs are usually associated with hemorrhagic pancreatitis but are not specific to haemorrhage (Meyers el., 1989; Mookadam and Cikes, 2005).

Around 10–20% AP patients have respiratory signs such as pleural effusion, left sided basal collapse, basal crepitations and wheezing (Baker, 2004).

Biochemical changes in acute pancreatitis (Table 1)

Table 1 – Biochemical changes in acute pancreatitis

Test	Specificity (SP) and sensitivity (SN)	Significances	False positive/false negative results
Serum lipase	Specificity is > 95% when lipase value > 600 IU/l. Overall (when value > 3 times of ULN) SN and SP are 80 to 100% and 50 to 99% respectively.	A. Lipase has a higher diagnostic accuracy compared to amylase. B. Elevated serum triglyceride level does not influence the serum lipase level as happens in the case of serum amylase. C. Pancreas is the only source of lipase.	False positive result can be seen in following conditions: 1. Inflammatory bowel disease 2. Renal insufficiency 3. Appendicitis 4. Intestinal ischemia 5. Intestinal obstruction 6. Intestinal perforation 7. Acute cholecystitis 8. Furosemide use
Serum amylase	Serum amylase cut-off level of 1000 IU/l has 55–84% sensitivity and specificity up to 95%.	A. Serum amylase level at least three times the upper limit of normal supports the diagnosis of acute pancreatitis. B. Synthesized by pancreas and salivary glands and in very small quantities from other locations such as fallopian tubes, testes, lungs, thyroid, tonsils, breast milk, sweat, tears, and some malignant neoplasm. C. In acute pancreatitis, serum amylase level increases quickly within six hours of onset of disease and returns to normal within 3 to 5 days, finally is excreted by the kidney.	False positive results can be seen in following conditions: 1. Macroamylasemia 2. Renal failure 3. Oesophageal perforation 4. Mumps parotitis 5. Pregnancy 6. Chronic alcoholism 7. Post coronary bypass 8. Lactic acidosis 9. Anorexia nervosa or bulimia False negative results (in 19–32% of cases)can be seen in following conditions: 1. Secondary to chronic alcohol abuse due to pre-existing pancreatic injury 2. Hypertriglyceridemia due to dilutional effects of the lipemia.

Trypsinogen (TAP)	Less commonly used in routine clinical practice due to its low sensitivity, specificity and limited availability.	A. The negative predictive value of urinary TAP is 99%, therefore negative test result can exclude diagnosis of acute pancreatitis. B. Both serum and urine concentrations of trypsinogen rise within few hours of onset of acute pancreatitis and come to normal level within 3 to 5 days.
Hepatic trans-aminases		Elevated in patients with acute pancreatitis caused by alcohol abuse or biliary pancreatitis. 1. Serum alanine aminotransferase (ALT) level higher than threefold or more above normal suggests biliary rather than alcoholic pancreatitis. 2. ALT level higher than 150 IU/l has 95% positive predictive value in diagnosing gallstone pancreatitis.
WBC count, CRP		Both are elevated due to systemic inflammatory response in early course of acute AP. However elevation of WBC count and CRP after 7–10 days of onset (late phase of AP) indicate infection.
Serum calcium and trigly-ceride level		Advised to identify underlying cause of acute pancreatitis.

Serum lipase

Due to its high sensitivity and specificity, serum lipase is the primary diagnostic serum marker of acute pancreatitis. The specificity (50% to 99%) and sensitivity (86% to 100%) of lipase are greater than amylase for diagnosis of AP (Gamaste, 1994). Lipase has a higher diagnostic accuracy compared to amylase as the half-life of elevated amylase is shorter than that of lipase (Matull et al., 2006) and the pancreas is the only source of lipase. The specificity of lipase is improved by increasing the threshold to at least three times the upper limit of the normal reference values (Calleja and Barkin, 1993). At lipase cut-off level of 600 IU/l, reported specificity is above 95% (Kylänpää-Bäck et al., 2002; Matull et al., 2006). Concentration of lipase in serum increases within 3–6 hours after onset of AP, peaks within 24 hours and stays around 1–2 weeks before it comes down to the normal level (Matull et al., 2006; Lippi et al., 2012). Lipase is preferred over amylase in routine clinical practice (Forsmark and Baillie, 2007). Elevated serum triglyceride level does not influence

the serum lipase level as happens in the case of serum amylase. Some medical and surgical conditions such as inflammatory bowel disease, renal insufficiency, appendicitis, intestinal ischemia, obstruction, perforation, acute cholecystitis may give false positive result (Matull et al., 2006; Lippi et al., 2012; Meher et al., 2015). Drug such as furosemide also can increase serum lipase level (Matull et al., 2006).

Serum amylase

Amylase is a glycoside hydrolase primarily synthesized by pancreas and salivary glands and in very small quantities from other locations such as fallopian tubes, testes, lungs, thyroid, tonsils, breast milk, sweat, tears, and some malignant neoplasms. Electrophoresis shows that serum amylase is of two main types such as P-type amylase from the pancreas, and S-type amylase from the salivary glands. Serum amylase level at least three times the upper limit of normal supports the diagnosis of acute pancreatitis. In acute pancreatitis, serum amylase level increases quickly within six hours of onset of disease and returns to normal within 3 to 5 days, finally is excreted by the kidney (Smotkin and Tenner, 2002; Rau et al., 2005; Shah et al., 2010). Serum amylase activity is normal or low in 19–32% of cases at the time of hospital admission, secondary to chronic alcohol abuse due to pre-existing pancreatic injury (Clavien et al., 1989; Matull et al., 2006) and hypertriglyceridemia due to dilutional effects of the lipemia (Yadav et al., 2002; Matull et al., 2006). Sensitivity and specificity of serum amylase value for diagnosis of AP depend on its threshold value, and a cut-off serum level of 1000 IU/l has 55–84% sensitivity and specificity up to 95% (Pieper-Bigelow et al., 1990; Keim et al., 1998; Smith et al., 2005). Other than acute pancreatitis, several conditions increase serum amylase level such as macroamylasemia, renal failure, oesophageal perforation, mumps parotitis, pregnancy, chronic alcoholism, post coronary bypass, lactic acidosis, anorexia nervosa or bulimia (Pieper-Bigelow et al., 1990; Cappell, 2008). Serum amylase is being used since a long time for the diagnosis of AP because it is the only biochemical marker available in many small hospitals.

Trypsinogen

Trypsinogen (TAP) is useful as a diagnostic marker for acute pancreatitis due to their accuracy, but its use is limited by availability (Matull et al., 2006). Among two isoenzymes of trypsinogen, trypsinogen-2 shows considerably higher serum concentrations in AP (Petersson et al., 1999). Both serum and urine concentrations of trypsinogen rise within few hours of onset of acute pancreatitis and come to normal level within 3 to 5 days (Petersson et al., 1999; Matull et al., 2006; Lippi et al., 2012). Dipstick method to detect urinary trysinogen-2 may be devised for rapid detection of AP but this method is less commonly used in routine clinical practice due to its low sensitivity, specificity and limited availability (Kamer et al., 2007; Lippi et al., 2012). Early elevated levels of urinary TAP are associated with severe acute pancreatitis (Toouli et al., 2002). The negative predictive value of urinary TAP is

99%, so negative test result can exclude diagnosis of acute pancreatitis (Kemppainen et al., 1997).

Other biochemical markers

Leukocytosis is common laboratory finding of AP in early course due to systemic inflammatory response but in later stage (7 to 10 days after onset of AP) it indicates infection. Hepatic transaminases level may be elevated in patients with pancreatitis caused by alcohol abuse or biliary pancreatitis. Around 20% of AP patients have jaundice and jaundice associated with pancreatitis in the absence of choledocholithiasis usually is related to hepatocellular involvement (McCollum and Jordan, 1975). Serum alanine aminotransferases (ALT) level higher than threefold or more above normal suggests biliary rather than alcoholic pancreatitis (Ammori et al., 2003) and ALT level higher than 150 IU/l has 95% positive predictive value in diagnosing gallstone pancreatitis (Tenner et al., 1994). Mild elevation of blood sugar level is also seen due to decreased insulin secretion and increased glucagon levels. Serum calcium and triglyceride level should be advised to identify underlying cause of acute pancreatitis.

Imagines for diagnosis of acute pancreatitis

According to the Revised Atlanta classification (2012), imaging is used in diagnosis of AP. Imaging is manifold to clarify the diagnosis of AP when the clinical picture is confusing (when abdominal pain is suggestive of acute pancreatitis but the serum amylase or lipase assay is less than 3 times the upper limit of normal) (Bollen, 2012).

Ultrasound is frequently used as the first investigation on admission although it has limited value in the diagnosis of pancreatitis or its complications (Koo et al., 2010) and may show pancreatic swelling but in only 25–50% of patients with acute pancreatitis, pancreas is visualised. Pancreas is obscured secondary to bowel gas in 35% cases during ultrasonography (Gamaste, 1994). The most common cause of acute pancreatitis is cholelithiasis followed by alcohol intake therefore to detect cholelithiasis transabdominal ultrasonography should be performed for all patients at admission (Van Santvoort et al., 2011; Working Group IAPAPAAPG, 2013). For the detection of cholelithiasis, sensitivity of abdominal ultrasonography is 95% but sensitive for the detection of choledocholithiasis (bile duct stone) is 50% (O'Connor et al., 1986).

Among all imaging modalities, contrast enhanced CT (CECT) is the standard technique for overall assessment of acute pancreatitis and its sequelae (Fisher and Gardner, 2012; Johnson et al., 2014; Zhao et al., 2015). For visualization of pancreatic pathology, contrast enhanced computed tomography (CT scan) and magnetic resonance imaging (MRI) of the abdomen are best imaging modalities, although these investigations are not routinely indicated in patients with mild AP. CECT abdomen is more accurate than ultrasonography for detection of

peripancreatic inflammation and intrapancreatic necrosis. CT abdomen should be done in patients who present with severe pancreatitis or present initially with mild to moderate pancreatitis but does not improve after several days of supportive therapy. However CECT is contraindicated in patients who have intravenous contrast allergy or renal insufficiency.

MRI abdomen is usually advised those who are pregnant (to avoid radiation from CT), allergic to the contrast used for enhanced CT, and have renal insufficiency (Zhao et al., 2015). Magnetic resonance cholangiopancreatography (MRCP) abdomen is also indicated in patients who have altered liver function tests (LFT) with suspected common bile duct stone or disease but ultrasonography is inconclusive.

Sensitivity of endoscopic ultrasound (EUS) is greater than MRCP for detection of common bile duct stone. EUS is usually advised in patients who are pregnant because of its relative safety during pregnancy and in patients who cannot undergo MRCP due to presence of internal metallic devices (Cappell, 2008). It is the least expensive initial investigation for the diagnostic evaluation of patients with idiopathic acute pancreatitis with gallbladder *in situ* (Wilcox and Kilgore, 2009).

Endoscopic retrograde cholangiopancreatography (ERCP) can be used with extreme caution in acute pancreatitis patients and should never be used as a first-line diagnostic tool in AP (Telem et al., 2009). ERCP should be performed only when the patient has acute pancreatitis with cholangitis secondary to choledocholithiasis and when patient with biliary pancreatitis is experiencing worsening jaundice and clinical deterioration despite maximal supportive therapy (Kapetanos, 2010). There is no indication for urgent ERCP in patients with mild pancreatitis without cholangitis (Kapetanos, 2010).

Severity assessment

15–20% of acute pancreatitis patients develop severe disease and have prolonged hospital stay (Forsmark and Baillie, 2007; Tenner et al., 2013; Greenberg et al., 2016), and 20 to 30 percent of AP patients develop complications such as necrosis, organ failure, or both (Mayer et al., 1985; Thomson, 1985). It is very important to assess severity of acute pancreatitis as early as possible because morbidity and mortality of AP differ markedly between mild and severe disease (in mild disease < 5% vs. in severe disease 20–25%) (Tandon, 2013). Detection of severity of AP is important for early recognition of pancreatic complications, therapeutic decisions, triage of patients to higher levels of care such as an ICU, and prognostication.

There are several clinical, biochemical, radiological markers and scoring systems (Table 2) are available to detect severity of AP but clinical monitoring is inadequate to detect severity and predicting the course of acute pancreatitis because about only 39 percent of severe cases can be detected by clinical assessment (Ranson, 1985). There are no “gold standard” prognostic score to predict severe acute pancreatitis (Leppäniemi et al., 2019).

Table 2 – Different scoring systems for severity assessment of acute pancreatitis (AP)

Scoring system	Interpretation and mortality (MT)
1. Revised Atlanta classification (RAC) of acute pancreatitis	No organ failure and no systemic or local complications: mild acute pancreatitis (AP) (MT: 1–2%). Transient organ failure (<48 hours) and/or local or systemic complications: moderate AP (MT: ~2%). Persistent organ failure and/or local or systemic complications: severe AP (MT: 20–40%).
2. Determinant based classification (DBC) of AP	Mild AP: lacks of both (peri) pancreatic necrosis and organ failure. Moderate AP: sterile (peri) pancreatic necrosis and/or transient organ failure. Severe AP: presence of either infected (peri) pancreatic necrosis or persistent organ failure. Critical acute AP: infected (peri) pancreatic necrosis and persistent organ failure.
3. Ranson's criteria	Score ≥ 3: severe pancreatitis likely and score < 3: severe pancreatitis is unlikely. Score < 3: MT 0–3%; score 3–5: MT 11–15% and score ≥ 6: MT ~40%.
4. Modified Ranson's criteria	It has 10 parameters to assess gallstone pancreatitis.
5. BISAP (bedside index of severity in acute pancreatitis) score	Cut-off value of BISAP score for prediction of severe AP is ≥ 2. MT is < 2% when BISAP score 0–2 and > 15% when BISAP score 3–5.
6. APACHE II scale	APACHE II score is > 8 points; it is classified as severe acute pancreatitis. After 48 hours, the APACHE II score can predict the outcome in 88% of acute pancreatitis cases.
7. Glasgow score	There is a cut off for severe AP: ≥ 2 points and scores above 3 also indicate that the patient is likely to require admission to intensive care (ICU).
8. The harmless acute pancreatitis (HAP) score	HAP score is considered positive if patients have any of these three criteria. HAP score 0 indicates patients do not require early aggressive treatments and advanced radiological screening during the initial stages of the AP.
9. The new Japanese severity scoring system for AP (Japanese severity score for acute pancreatitis)	Severe AP is diagnosed when the total prognostic factor score is ≥ 3. Prognostic factor score ≥ 4 is the best cut-off value to identify patients who were at risk for mortality.
10. PANC3 score	The combination of the PANC3 variables was highly predictive of SAP. (96.43% specificity, 75% sensitivity, 80% positive predictive value, and 95.29% negative predictive value to identify severe acute pancreatitis).

11. PANC4 score	It needs further large studies to prove good results in large scale and its use in clinical practice.
12. CT severity index (CTSI)	Mild AP (CTSI: 0–3), moderate AP (CTSI: 4–6), severe AP (CTSI: 7–10; MT 17%)
13. Modified computed tomography severity index (MCTSI)	Mild AP (score: 0–2), moderate AP (score: 4–6), severe AP (score: 8–10)

Revised Atlanta classification (RAC) of acute pancreatitis

This system classifies AP into three groups based on presence or absence of persistent organ failure and local and systemic complications. Mild AP is defined as no organ failure and no systemic or local complications, and is associated with rare mortality (1–2%) (Triester and Kowdley, 2002). Moderately severe AP has transient organ failure (<48 hours) and/or local or systemic complications and is associated with a low mortality rate of approximately 2% (Vege et al., 2009) and severe AP has persistent organ failure and/or local or systemic complications with a mortality rate of approximately 20–40% (Sarr, 2013; Talukdar et al., 2014a; Meher et al., 2015). The modified Marshall scoring system is used in the Revised Atlanta classification as the primary method to detect organ failure and includes measurements from the respiratory (PaO_2/FiO_2 ratio) (score 1: 301–400, score 2: 201–300, score 3: 101–200, score 4: ≤ 100), cardiovascular (systolic blood pressure) (score 1: < 90 mm Hg but responding to fluid resuscitation therapy, score 2: < 90 mm Hg but not responding to fluid resuscitation therapy, score 3: < 90 mm Hg and pH < 7.3, score 4: < 90 mm Hg and pH < 7.2), and renal systems (creatinine value) (score 1: 1.5–1.8 mg/dl, score 2: 1.9–3.5 mg/dl, score 3: 3.6–4.9 mg/dl), with a score of 2 or higher for any system indicating organ failure (Marshall et al., 1995; Thoeni, 2012; Banks et al., 2013). Local complications are fluid collections (acute peripancreatic fluid collection, pancreatic pseudocyst, acute necrotic collection, and walled off necrosis), gastric outlet dysfunction, spleenic vein thrombosis, portal vein thrombosis, and colonic necrosis (Banks et al., 2013; Sarr, 2013). Systemic complication is defined as renal, circulatory, or respiratory organ failure or exacerbation of pre-existing comorbidities like coronary artery disease, congestive cardiac failure, chronic obstructive pulmonary disease, diabetes, and chronic liver disease due to acute pancreatitis (Sarr, 2013). The Revised Atlanta classification (RAC) divides course of AP into an early phase, usually lasting up to 1 week, followed by a late phase which is characterized by persistent signs and symptoms with systemic or local complications, occurring only in moderately severe and severe AP and lasting > 1 week and can extend for months.

Determinant based classification (DBC) of AP

The primary highlight of the determinant based classification (DBC) is the introduction of the new group called critical acute pancreatitis. The severity of AP is classified into four categories based on DBC (mild, moderate, severe, and critical AP). Mild AP lacks both (peri) pancreatic necrosis and organ failure. Moderate AP has sterile (peri) pancreatic necrosis and/or transient organ failure. Severe AP is defined as the presence of either infected (peri) pancreatic necrosis or persistent organ failure (Dellinger et al., 2012). When AP has both infected (peri) pancreatic necrosis and persistent organ failure, it is called critical acute pancreatitis. DBC system has less heterogeneity than RAC system with respect to classification of moderate acute pancreatitis, which should be noted when using RAC to classify acute pancreatitis (Qi et al., 2017).

Ranson's criteria

The Ranson's criterion is a scoring system to predict severity and mortality of acute pancreatitis. Dr. John Ranson, a surgeon introduced this criterion in 1974 in his article "Prognostic signs and the role of operative management in acute pancreatitis".

Variables in Ranson's criteria: the score takes 11 variables: 5 of which (patient older than 55 years, WBC count higher than 16,000/µl, blood glucose level higher than 200 mg/dl, serum LDH level higher than 350 IU/l, AST level higher than 250 IU/l) are measured at the time of admission while 6 of these (hematocrit fall of more than 10%, BUN level increase by more than 8 mg/dl, serum calcium level lower than 8 mg/dl, PaO_2 less than 60 mm Hg, base deficit higher than 4 mEq/l, estimated fluid sequestration > 6 liters) are measured 48 h after admission (Imrie, 2003).

Interpretations of Ranson's criteria: if the score ≥ 3, severe pancreatitis likely and if the score < 3, severe pancreatitis is unlikely (Ranson, 1982; Ducarme et al., 2014). The mortality rises with increasing total scores, 0–3% mortality in patients with a score < 3, 11–15% in a score ≥ 3, and 40% when the score is ≥ 6 (Banks et al., 2006).

Limitations of Ranson's criteria: 1) The Ranson score is valid only at 48 hours after onset of AP. 2) Other scoring systems are superior to Ranson's criteria in either sensitivity or specificity. Sensitivity of Ranson's score is only 73% and the specificity is 77% for predicting mortality. 3) Ranson's criteria cannot be used for a paediatric or adolescent population because Ranson et al. included an age range of approximately 30 to 75 years old in their study (Lautz et al., 2011). 4) Threshold for an abnormal value for alcoholic and gall stone pancreatitis are not same. 5) It is a poor predictor of severity (Papachristou et al., 2010).

Modified Ranson's criteria

The Ranson's criteria are used to score alcoholic pancreatitis while the modified criteria including 10 parameters are used to score gallbladder pancreatitis (Shah

et al., 2017; Hagjer and Kumar, 2018; Waller et al., 2018). It has 10 parameters to assess gallstone pancreatitis. Five parameters assessed on admission and the other five at the 48-hour after admission.

BISAP (bedside index of severity in acute pancreatitis) score

This scoring system is easy to use but has only been validated to predict mortality (Papachristou et al., 2010; Gao et al., 2015). BISAP scoring system is not inferior to Ranson's scoring system to predict severity of acute pancreatitis (Parimala and Beulah, 2019). Ranson's scores identify severe acute pancreatitis (SAP) more accurately than BISAP scores (97.4% vs. 69.2%) and specificity of both scores predicts SAP almost equally (78.4% vs. 77.8%) (Arif et al., 2019). However another study (systemic review and meta-analysis) showed that compared with BISAP score, the Ranson criteria and APACHE II score have higher sensitivity and lower specificity to predict both severe acute pancreatitis and mortality (Gao et al., 2015).

This score is one of the most accurate and applicable in everyday clinical practice because of the simplicity and the capability to predict severity, death, and organ failure (Leppäniemi et al., 2019). BISAP score has fewer variables than Ranson's score and APACHE II score and is cost effective and can be calculated in emergency setting, so; there is no time delay (Arif et al., 2019). It is a reliable scoring system to predict severity and organ failure within 24 hours of admission (Kaushik et al., 2017).

BISAP scoring system includes following components: BUN > 25 mg/dl, impaired mental status (Glasgow coma scale < 15), SIRS (it is defined as two or more of the following: 1) temperature of >38.0 °C or <36.0 °C, 2) respiratory rate > 24 breaths/min or $PaCO_2$ < 32 mm Hg, 3) pulse > 90 beats/min, 4) WBC 12,000 cells/mm^3 or > 10% immature bands), age > 60 years, pleural effusion detected on chest radiograph.

Cut-off value of BISAP score for prediction of severe AP is ≥ 2 (Cho et al., 2015). Another meta-analysis showed that a BISAP score of 3 is reliable to identify the high-risk AP (Gao et al., 2015). BISAP score showed mortality of < 2% when score: 0–2 and > 15% when score: 3–5 (Wu et al., 2018). One study from China demonstrated that the best cut-off value for BISAP is 2 for predicting pancreatic necrosis and organ failure, and 3 for predicting mortality (Chen et al., 2013).

APACHE II scale

It can be performed on admission and re-evaluated at any time during the hospitalization. APACHE II score includes 11 physiologic components plus patient's age, organ insufficiency, neurologic status and postoperative state (Cappell, 2008). Due to its complicated nature and requirement of long list of parameters, it is not practical to use in smaller hospitals with limited staff and expertise. After 48 hours, the APACHE II score can predict the outcome in 88% of acute pancreatitis cases (Larvin and McMahon, 1989).

According to Atlanta Symposium (1992) (Bradley, 1993) and the World Congress of Gastroenterology Guidelines (2002) (Toouli et al., 2002), when APACHE II score is > 8 points; it is classified as severe acute pancreatitis.

Glasgow score

The Glasgow pancreatitis score was created by Blamey et al. in 1984 as a prognostic factor to identify the severity of AP. It is also called Imrie score and includes eight of 11 variables used in the Ranson's criteria, and can be performed within 24 hours from admission for patients.

This scoring system includes following components: 1) age > 55 years, 2) serum albumin < 32 g/l (3.2 g/dl), 3) arterial PO_2 on room air < 8 kPa (60 mm Hg), 4) serum calcium < 2 mmols/l (8 mg/dl), 5) blood glucose > 10.0 mmols/l (180 mg/dl), 6) serum LDH > 600 units/l, 7) serum urea nitrogen > 16.1 mmols/l (45 mg/dl), 8) WBC count > 15×10^9/l (15×10^3/microlitre).

Each variable in this scoring system has 1 point. Cut-off for severe AP is ≥ 2 points, and scores above 3 also indicate that the patient is likely to require admission to intensive care (ICU) (Blamey et al., 1984; Taylor et al., 2005; Mounzer et al., 2012).

The harmless acute pancreatitis (HAP) score

This is a simple and useful scoring algorithm which requires three parameters to identify patients with nonsevere AP. HAP score can predict a non-severe course within 30–60 min of admission (Lankisch et al., 2009; Talukdar et al., 2014b). This scoring system has high specificity (97%) and positive predictive value (98%) and allows physicians to detect AP patients quickly who do not require ICU care, and potentially those who do not require inpatient treatment at all, and reduce hospital cost (Lankisch et al., 2009).

HAP score includes three parameters: rebound abdominal tenderness and/or guarding, serum creatinine serum creatinine of > 2 mg/dl, and hematocrit of > 43 for male and > 39.6 for female patients, at the time of admission. HAP score is considered positive if patients have any of these three criteria. Presence of each of these is awarded a score of 1, thus minimum score is 0 and a maximum score is 3 (Talukdar et al., 2014a; Sayraç et al., 2018). HAP score 0 indicates patients do not require early aggressive treatments and advanced radiological screening during the initial stages of the AP (Sayraç et al., 2018).

The new Japanese severity scoring system for AP (Japanese severity score for acute pancreatitis)

This score has good predictive value for in-hospital mortality of acute pancreatitis patients, and is useful for severity assessment of AP at the initial stage of hospital admission (Hamada et al., 2013). It includes nine clinical and biochemical parameters and total score using a scale of 0–9 (Yokoe et al., 2015).

Based on the Japanese severity criteria, severe AP is diagnosed when the total prognostic factor score is ≥ 3 or the contrast-enhanced CT grade is ≥ 2 (Ikeura et al., 2017). Prognostic factor score ≥ 4 is the best cut-off value to identify patients who were at risk for mortality (Ikeura et al., 2017). The Japanese severity scoring system can be considered non-inferior to Ranson's score, Glasgow score, and APACHE II score for predicting mortality (Ueda et al., 2009; Hamada et al., 2013).

PANC3 score

This scoring system is simple, easy to assess, readily available, and economic. It includes three factors: serum hematocrit greater than 44 mg/dl, a body mass index (BMI) greater than 30 mg/kg, and a chest X-ray which reveals a pleural effusion (Brown et al., 2007). According to Brown et al. (2007), serum hematocrit is the strongest predictor of SAP and found that all three factors combined had a post-test likelihood ratio of 99% of developing severe acute pancreatitis. The combination of the three variables is highly predictive of SAP. PANC3 score has 96.43% specificity, 75% sensitivity, 80% positive predictive value, and 95.29% negative predictive value to identify severe acute pancreatitis (Shah et al., 2017). Another study showed that PANC3 score has sensitivity of 33% and specificity of 100% (Borges et al., 2017).

PANC4 score

PANC4 criterion (two PANC3 markers + urea + platelets / leukocytes) proposed by Borges et al. (2017) is a score for the prognosis and severity of acute pancreatitis, but it needs further large studies to prove good results in large scale and its use in clinical practice.

Amylase and BMI (CAB) score

It is developed to identify patients most likely to develop severe AP based on the percentage changes in serum level of amylase during the first 2 days after admission to the hospital and BMI (Kumaravel et al., 2015).

Single markers for predicting ASP

1) On admission, hematocrit value ≥ 44% or failure of the hematocrit to decrease at 24 hours after admission is an indicative of SAP in the early stage of the disease (Berger and Rau, 2007). Absence of hemoconcentration on admission has a high negative predictive value for the necrosis development after AP (Gardner et al., 2006). 2) Serum creatinine is a predictor for pancreatic necrosis and an estimated glomerular filtration rate (GFR) < 90 ml/min per 1.73 m^2 on admission can predict pancreatic necrosis (Muddana et al., 2009; Lipinski et al., 2013). 3) Rise in BUN > 1.8 mmol/l after 48 hours have a high predictive value as a single parameter SAP (Wu et al., 2011). 4) Rise of C- reactive protein (CRP) > 90 mg/dl from admission or an absolute value of > 190 mg/dl at 48 h predicts severe AP with the greatest accuracy (Stirling et al., 2017). C-reactive protein > 150 mg/l can predict

complications in acute pancreatitis. 5) Procalcitonin (PCT) has been proposed to be useful marker for the detection of bacterial contamination of pancreatic necrosis (Rau et al., 1997) and a rapid semiquantitative PCT-assay is suggested to be valuable in differentiating severe AP from and mild cases (Wereszczynska et al., 1998). 6) Serum amylase and lipase are poor predictors of severity of AP (Swaroop et al., 2004). 7) Blood glucose concentration < 6.9 mmol/l on admission has a high negative predictive value (92%) for pancreatic necrosis and also can serve as a predictor for severity of AP (Lankisch et al., 2001; Rajaratnam and Martin, 2006).

CT severity index (CTSI)

Optimal timing for initial CT assessment in AP is at least 72–96 hours after onset of symptoms. Recommendation is to perform multidetector CT with thin collimation and slice thickness (i.e. 5 mm or less), 100–150 ml of non-ionic intra-venous contrast material at a rate of 3 ml/s, during the pancreatic and/or portal venous phase (i.e. 50–70 seconds delay) (Working Group IAPAPAAPG, 2013).

The Balthazar score (1985) categorizes patients with AP into 5 groups (A to E) according to pancreatic and peripancreatic changes diagnosed by non-contrast CT abdomen (Balthazar et al., 1985). The use of CECT to localization of site and/or extent of pancreatic necrosis enhances the accuracy in prediction of outcome and high CTSI score correlates with worsening severity and prognosis, pancreatic infection (Balthazar et al., 1990; Simchuk et al., 2000). CTSI includes Balthazar score and extent of pancreatic necrosis (score 0: no necrosis, score 1: < 30% necrosis, score 2: 30–50% necrosis and score 3: > 50% necrosis).

CT severity index of 0 or 1 exhibits 0% mortality rate and no morbidity, while patients with CTSI of 2 has no mortality and 4% morbidity rate, and CTSI of 7–10 has a 17% mortality rate and 92% complication rate (Balthazar et al., 1990). Depending on score, pancreatitis is divided into mild (score: 0–3), moderate (score: 4–6), severe (score: 7–10) (Balthazar et al., 1990).

Modified computed tomography severity index (MCTSI)

This index was developed on 2004. It includes pancreatic swelling or fat stranding, pancreatic collection(s), presence and extent of parenchymal necrosis, extrapancreatic complications including vascular, parenchymal, gastrointestinal organs and pleural effusion and ascites.

Score ranges from 0 to 10. Depending on score, pancreatitis is divided into mild (score: 0–2), moderate (score: 4–6), severe (score: 8–10) (Mortele et al., 2004).

The MCTSI correlates more closely with patient outcome measures than the CTSI, with similar inter-observer variability (Sahu et al., 2017). MCTSI has a higher sensitivity but lower specificity than CTSI in differentiating mild from moderate and severe acute pancreatitis and also showed significant correlation with clinical outcome parameters, and good concordance with revised Atlanta classification grading of severity (Sahu et al., 2017).

Others radiological index

Several other scores such as pancreatic size index (PSI), mesenteric edema and peritoneal fluid (MOP) score, extrapancreatic (EP) score, extrapancreatic inflammation on CT (EPIC) score, and MR severity index (MRSI) have been evaluated but none of these radiological scoring system were shown to be superior to clinical scoring systems (Tang et al., 2011; Bollen et al., 2012).

Conclusion

Acute pancreatitis is a potentially fatal disease, with mortality rates ranging from 0 to 25 percent, depending on severity. Therefore, early diagnosis of AP and severity assessment is important part of management. Revised Atlanta classification (2012) is commonly used for diagnosis of acute pancreatitis in day to day clinical practice. Once the diagnosis of AP is made, clinical efforts should simultaneously concentrate on investigating for the underlying aetiology and to find out severity of disease. In every-day clinical practice, Revised Atlanta classification system, BISAP score, HAP score, CT severity index can be used to assess severity of AP because these scoring systems can be measured at bedside and needs limited components. Severity assessment is initial main part of AP management because treatment of AP depends on grade of severity and aetiology.

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Osteoarthrosis: Analyze of the Molar Bite Force, Thickness and Masticatory Efficiency

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Abstract: Osteoarthrosis is a disorder of synovial joints, resulting from destruction of the cartilage and subchondral bone. The present study is aimed to investigate the molar bite force, thickness and efficiency of the masseter and temporalis muscles of subjects with osteoarthrosis. A total of forty-eight subjects participated in the study. They were distributed into two groups: with osteoarthrosis (n=24) and asymptomatic controls (n=24). Subjects were analyzed on the basis of maximal molar bite force (right and left side), thickness (mandibular rest and dental clenching in maximal voluntary contraction) and electromyographic activity of masticatory cycles through the linear envelope integral in habitual (raisins and peanuts) and non-habitual (Parafilm M) chewing of the masseter and temporalis muscles. All the data were analyzed statistically using *t*-test with a significance level of $p \leq 0.05$. There was no difference between groups in maximal molar bite force, muscle thickness and non-habitual chewing. Differences were found on the raisins ($p=0.02$) and peanuts ($p=0.05$) chewing for right temporal muscle, with reduced masticatory

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muscle efficiency in osteoarthrosis subjects. This study showed that osteoarthrosis induces negative changes in habitual chewing, highlighting the efficiency of the right temporalis muscles. The greater temporal muscle activity in subjects with osteoarthrosis may compromise chewing and consequently the nutritional status of adult subjects.

Introduction

Osteoarthrosis is a degenerative joint disease with slow progression characterized by attacks the synovial joints, involved in the stomatognathic system, particularly in the temporomandibular joints, by the sequel of displacement and perforation of the disc (Levorová et al., 2016). It is characterized by the destruction or alteration of articular cartilage with resultant bone repercussions (Mau-Moeller et al., 2017).

Clinically it can be defined by an insufficiency of the articular cartilage, resulting from mechanical, genetic, hormonal, bone or metabolic factors. These causes lead to an imbalance between the synthesis and degradation of articular cartilage and the subchondral bone (Camanho et al., 2011). This disease causes functional changes in 15% of the worldwide adult population, affecting subjects mainly subjects over 60 years old (Santos et al., 2014).

The temporomandibular joint is a part of the stomatognathic system, together with the bones, muscles, teeth, lips, tongue, cheeks, glands, arteries, veins and nerves. The structures of this system act together in such a way that any specific anatomical or functional modification can lead to an imbalance (Mupparapu et al., 2019).

Alterations in the components of the stomatognathic system, and specifically in the case of the temporomandibular joint, can lead to the development of temporomandibular disorders (Smaglyuk and Liakhovska, 2019). As such, this system has been the focus of several studies, mainly in groups of subjects with systemic pathological alterations similar to osteoarthrosis (Palinkas et al., 2018).

The null hypothesis of this study was that osteoarthrosis in its initial phase would not influence molar bite force, muscle thickness and efficiency of masticatory muscles, thus not interfering with the functioning of the stomatognathic system. The objective of this study was to verify whether osteoarthrosis causes functional alterations in the stomatognathic system of subjects with an initial diagnosis of the disease, when compared with subjects without osteoarthrosis.

Material and Methods

Study population

This study was approved by the Research Ethics (protocol #.55505316.8.0000.5419). All the subjects signed the free and informed consent. The subjects were diagnosed by a rheumatologist, following the guidelines of the American College of Rheumatology and recruited from specialized referral

centers for the treatment of chronic degenerative diseases in the cities of Batatais, Bebedouro and Ribeirão Preto, São Paulo, Brazil.

The post hoc sample size was calculated based on an error of 10% ($\alpha = 0.10$), and a power test of 85% for the main result of the electromyographic activity in the condition of raisin chewing (average values of the right temporal muscle). The value for the group with osteoarthrosis was 1.27 (0.86) and for the control group it was 0.81 (0.43) and the effect size was 0.67. The minimum sample size was 48 subjects (24 for each group). The sample size was calculated using the free-access software program G* Power version 3.1.9.2 (Franz Faul, Kiel University, Kiel, Germany).

A total of 72 subjects of both genders, aged between 40 and 70 years, were selected. In accordance with the inclusion and exclusion criteria, a final 12 subjects were selected for the group with osteoarthrosis (n=24; mean ± SD: 53.6 ± 1.6 years and 28.61 ± 0.98 kg/m^2), Angle Class I, contact pattern in maximum intercuspal position with tooth to two tooth occlusion and presence of all permanent teeth (except third molars) were selected. The disease-free group (n=24; average ± SD: 52.3 ± 1.7 years and 28.16 ± 0.78 kg/m^2) was composed of dentate individuals, without temporomandibular dysfunction (RDC/TMD) who were age-, gender-, weight-, and height-matched with subjects in the osteoarthrosis group.

The exclusion criteria involved absence of dental element (upper and lower); the temporomandibular dysfunction; presence of dental restorations with risk of fractures; and use of anti-inflammatories, analgesics and muscle relaxants that could interfere in neuromuscular physiology (da Silva et al., 2019).

Maximal bite force analysis

Digital dynamometer, model IDDK (Kratos, Cotia, São Paulo, Brazil), with a 1000 N capacity, adapted to the mouth was used for the molar bite force records. Three records were obtained of the molar bite force of the right and left molar region (Palinkas et al., 2010; Verri et al., 2019), alternating between the sides. There was a two-minute rest period between each measurement. The highest value out of three records was considered as the subject's maximal bite force (Castelo et al., 2010).

Ultrasound analysis

The portable ultrasound device (NanoMaxx; SonoSite Inc, Bothell, WA, USA) with 10 MHz linear-array transducer placed transversally was used to measure the thickness (centimeters) of the masseter and temporalis muscles fibers at rest and dental clenching in maximal voluntary contraction (Bertram et al., 2003), considering the bottom of the masseter muscle at 2.75 cm above the jaw angle toward the upper eyelid and the anterior temporalis muscle, and at 1.25 cm posterior and superior to the outside corner of the eye (da Silva et al., 2017). The location was confirmed by muscle palpation and movement of the linear transducer. For each clinical condition, three exams were conducted with an interval of 2 min between each acquisition.

Electromyographic analysis – efficiency

The electromyographic signals of the masticatory cycles (masseter and temporalis muscles) were collected using Trigno electromyography equipment (Delsys Inc., Boston, MA, USA), wireless surface electrodes, and followed the SENIAN (Surface Electromyography for the Non-Invasive Assessment of Muscles) guideline (Hermens et al., 2000).

Electromyographic recordings were performed of the masticatory cycles through the ensemble average analysis, which consists of using the integrated amplitude values of the linear envelopment of the masticatory cycles (Siéssere et al., 2009). The electromyographic signals were acquired in the habitual (raisins and peanuts) and non-habitual (Parafilm M) chewing. Parafilm M (Pechinery Plastic Packaging, Batavia, IL, USA) is constituted by a sheet of paraffin, which was folded (18 × 17 × 4 mm, weight 245 mg) placed on both sides of the dental arches.

During the non-habitual chewing, subjects were asked to make a movement of short opening to reduce the effects of the change in length × tension in the muscle, in typical dynamic records. The data of all the masticatory cycles were collected in 10 s.

Three initial masticatory cycles were excluded since, at the beginning of the masticatory process, the first cycles vary considerably during mandibular movements. Therefore, to calculate the results obtained in this study from the integral of the linear envelope of the masticatory cycles, the initial masticatory cycles were eliminated while the central cycles of the electromyographic were maintained (Siéssere et al., 2009; da Silva et al., 2017).

Statistical analysis

In the analysis of the results, the data showed normal distribution (Shapiro-Wilk normality test: $p \leq 0.05$). Data on maximal bite force, thickness and normalized electromyographic data were submitted to statistical analysis using IBM SPSS Statistics for Windows, version 22.0 (IBM SPSS, IBM Corp., Armonk, NY, USA). Results were obtained by descriptive analysis (mean and standard error) for each variable. Values were compared by using the Student's *t*-test, with statistical significance set at p-values < 0.05.

Results

No differences were found between groups in the maximal molar bite force (Table 1) and muscle thickness (Table 2) values. The standard electromyographic data for habitual (peanuts and raisins) and non-habitual (Parafilm M) chewing for the groups are shown in Table 3. Differences were found on the raisins ($p=0.02$) and peanuts ($p=0.05$) chewing for right temporal muscle, with reduced masticatory muscle efficiency in osteoarthrosis subjects.

Discussion

This study investigated the molar bite force, thickness and efficiency of the masseter and temporalis muscles of subjects with osteoarthrosis. In the present study, it was observed that there was no difference in comparisons between groups in the molar bite force (right and left), but it is documented that the higher the bite force, the better the performance of the masticatory muscles, and consequently an increased functional capacity of the stomatognathic system (Palinkas et al., 2016; Goiato et al., 2017). Although bite force results showed no difference in our study, it was evident that the function of the stomatognathic system of subjects with osteoarthrosis was compromised based on the results obtained in the masticatory efficiency analysis.

In this study, the position of the transducer was determined by the palpation of the muscles at rest and during maximal voluntary contraction (Levorová et al., 2016). This allowed us to obtain high quality images, and allowed us to identify the mandible branch, as well as the temporal bone. This ensured the correct collection and

Table 1 – Mean values (standard error) and statistical significance (p≤0.05) of the right and left molar bite force (Newton) for osteoarthrosis (OAG) and without the disease (CG) groups

Bite force	OAG	CG	P-value
Right molar	251 ± 21	281 ± 31	0.52
Left molar	260 ± 21	270 ± 30	0.83

Table 2 – Mean values (standard error) and statistical significance (p≤0.05) of the thickness (cm) of the right masseter (RM), left masseter (LM), right temporal (RT) and left temporal (LT) muscles at rest and maximal voluntary contraction (MCV) in osteoarthrosis disease (OAG) and without the disease (CG) groups

Mandibular tasks and muscles	OAG	CG	P-value
Rest			
RM	0.90 ± 0.06	0.81 ± 0.03	0.21
LM	0.90 ± 0.03	0.88 ± 0.03	0.70
RT	0.38 ± 0.02	0.39 ± 0.03	0.75
LT	0.36 ± 0.02	0.40 ± 0.02	0.21
MVC			
RM	1.27 ± 0.06	1.23 ± 0.04	0.65
LM	1.28 ± 0.06	1.27 ± 0.04	0.86
RT	0.48 ± 0.02	0.45 ± 0.02	0.38
LT	0.46 ± 0.02	0.56 ± 0.08	0.25

Table 3 – Mean values (standard error) of the normalized electromyographic data and statistical significance (p≤0.05)* of habitual and non-habitual chewing in osteoarthrosis disease (OAG) and without the disease (CG) groups for right masseter (RM), left masseter (LM), right temporal (RT) and left temporal (LT) muscles

Chewing	Muscles	Groups		P-value
		OAG	CG	
Peanuts	RM	0.85 ± 0.10	0.95 ± 0.09	0.35
	LM	0.86 ± 0.08	0.85 ± 0.09	0.91
	RT	1.08 ± 0.10	0.82 ± 0.81	0.05*
	LT	0.87 ± 0.09	0.86 ± 0.09	0.98
Raisins	RM	0.89 ± 0.11	0.74 ± 0.10	0.34
	LM	0.68 ± 0.09	0.80 ± 0.09	0.37
	RT	1.27 ± 0.17	0.82 ± 0.08	0.02*
	LT	0.91 ± 0.12	0.84 ± 0.08	0.61
Parafilm M	RM	0.80 ± 0.10	0.98 ± 0.09	0.21
	LM	0.85 ± 0.09	0.84 ± 0.09	0.80
	RT	0.90 ± 0.08	0.86 ± 0.08	0.80
	LT	0.80 ± 0.08	0.91 ± 0.06	0.30

measurement of the images of the masseter and temporalis muscles (Kubota et al., 1998). The thickness of the masseter and temporalis muscles of the subjects with osteoarthrosis in this study were not different when compared to the control group.

Our results are like the findings of Rodrigues et al. (2017) who analyzed subjects with rheumatoid arthritis. They also did not observe differences in the thickness of the masseter and temporal muscles in comparison with control subjects. Thus, these previous results agree with our current findings that subjects with osteoarthrosis show no presence of muscle hypertrophy or atrophy.

In the habitual chewing of raisins was observed functional alteration in masticatory efficiency, especially for the right temporal muscle. A greater recruitment of the fibers of the right temporal muscle was required in the subjects affected by osteoarthrosis, when compared to the group without the disease. The same result was also observed when we analyzed the habitual chewing of peanuts, with a significantly higher recruitment of the right temporalis muscle in the subjects affected by osteoarthrosis. Such a condition can lead to a decrease in masticatory efficiency and considerably more physical effort (Kumai, 1993; Gonçalves et al., 2018; da Silva et al., 2019).

Another hypothesis to explain our results in habitual chewing would be pathological changes in the temporomandibular joint of individuals with osteoarthritis such as synovial membrane hyperplasia, chronic inflammatory infiltrate, disorganization of the collagen fibers, greater thickness of the articular

disc, reduced of proteoglycans content, a decreased thickness of articular cartilage, lower feed intake, higher activity of metalloproteinases, and higher concentrations of interleukins and tumour necrosis factor α, which could promote negative functional changes in the stomatognathic system (Lemos et al., 2018). In this study it was not evaluated if the temporomandibular joint was affected with osteoarthritis.

In this study it was not evaluated if their subjects suffered from bilateral or unilateral osteoarthrosis and which side was affected, because there was no confirmation by looking at retrospective CT of the selected subjects (Lehman et al., 2009; Haj-Mirzaian et al., 2019). The use of retrospective computed tomography is recommended for the diagnosis of degenerative diseases of the temporomandibular joint to reduce false negatives which may be found by panoramic radiographs and magnetic resonance imaging (Kaimal et al., 2018).

This would probably be a factor that could explain the only significant result related to the finding of electromyographic activity in the right temporal muscle. This may suggest that the temporomandibular joint side possibly affected by osteoarthrosis reflects in the recruitment of motor units of the temporal muscle.

This same muscle also presented higher activity in the non-habitual chewing of Parafilm M, but without difference. The absence of difference may be related to reduced and controlled movement of the jaw in this clinical condition, decreasing the effects of changing length and muscle tension (De Luca, 1997).

In our study, masticatory activity was lower (electromyographic activity) when chewing of foods of soft consistency when compared with chewing foods of hard consistency. These results agree with those of Komino and Shiga (2017) who verified that the value of the masseter muscle envelope integral increased significantly as the amount of gelatine increased in the food (gum). That is, the harder the food, the higher the activity required by the muscle.

The limitations of this study are as follows. First, we did not use retrospective computed tomography to determine if there was involvement of the temporomandibular joint and other structural components of this joint in subjects with the initial stages of osteoarthrosis. Secondly, our sample selection of subjects with osteoarthrosis in the initial phase may be a limitation, given that it could influence the absence of severe alterations in reflexes, muscle strength or muscle thickness. As such, future studies should be designed specifically to address these problems.

Given the results of this study, we reject our null hypothesis as, even in the initial phase; osteoarthrosis had a negative impact on the subjects' lives and caused significant alterations in the electrical activity of the musculature analyzed during masticatory efficiency.

Conclusion

The results suggest that osteoarthrosis induces negative changes in habitual chewing highlighting the efficiency of the right temporalis muscles.

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Discectomy with Subsequent Free Fat Flap Insertion in Disc Perforation Therapy of Temporomandibular Joint. Assessment of Results 24 Months after Operation

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Key words: Discectomy – Disc perforation – Free fat flap – Temporomandibular joint

Abstract: Discectomy with replacement of disc is one possibility for treating disc perforation where conservative, mini-invasive therapy and arthroscopy has had no effect. Allogenic or autologous materials are used to replace the disc. The authors assess the use of a free fat flap (FFF) in 19 patients who in 2015–2016 underwent a unilateral discectomy with disc replacement. In the retrospective 24-month follow-up study a total of 16 patients (84%) were free of difficulties. 24 months after the operation mouth opening was on average 39.3 mm, pain (VAS – visual analog scale (0–10) was assessed on average at 0.3). Crepitus was present after 24 months in 37.5% of patients (6 patients). An assessment of changes in joint structures on cone beam computed tomography (CBCT) for these patients 24 months after the operation showed the progression of flattening of the joint head, in one case unevenness of the joint head. In 3 cases (16%) there was a recurrence of the state within 24 months – in all cases with clinical manifestations of pain and limited mobility, for these patients on the CBCT significant unevennesses of the joint head, subchondral cysts were noted. The authors find discectomy with use of FFF to be an effective method of treatment with a minimum of complications. However, one should take into account the relatively short time of monitoring after the operation (2 years) and limited number of patients in the cohort (19 patients).

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Introduction

Perforation of the disc of the temporomandibular joint occurs as a result of degenerative changes, and it can be divided into central (localised in the area of the actual disc) and peripheral (which occurs in the transitional zone, at the insertion point of the retrodiscal tissue on the disc). Disc perforations are accompanied by many clinical signs (crepitus during jaw movement, pain, limitation of jaw mobility). They can also be completely asymptomatic. Asymptomatic perforation is not an indication for therapy – objective and subjective difficulties of the patient constitute an indication. Diagnosis of perforation relies on magnetic resonance imaging (MRI), but the most accurate diagnostic method for confirming perforation is arthroscopy (ASC) (Laskin et al., 2006; Machon et al., 2017). An arthroscopic lavage is a successful treatment method, as confirmed by the authors in their previous work (Machon et al., 2017). If the arthroscopy has no effect, in the case of disc perforation the disc is removed and possibly replaced (but only if at the same time only slight changes in the joint head and fossa are present). If as well as disc perforation there are extensive degenerative changes to the condyle or fossa (erosion, subchondral cysts), in addition to a discectomy it is possible to carry out at the same time a resection of the condyle with subsequent total joint replacement (Mercuri, 2008; Machoň, 2017).

The specified materials (allogenic or autologous) for replacement of the disc are: silicone sheets, autogenous dermal graft, dermis-fat graft, auricular cartilage graft, temporoparietal fascia flap, and temporalis myofascial flap, free fat flap) (Dimitroulis, 2011; DeMerle et al., 2017).

The aim of the authors' work is to evaluate the effect of a discectomy with subsequent insertion of free fat flap into the joint cavity in a 2-year retrospective study.

Material and Methods

The cohort consisted of 19 patients (in all cases they were women, the average age was 53.7, the ages ranged from 20 to 71). The cohort included only patients with unilateral disc perforation who in the years 2015–2016 had undergone arthroscopic lavage following previous ineffective conservative therapy. Patients with a bilateral

Table 1 – Symptoms of patients indicated for discectomy with subsequent use of FFF

Symptoms	
Limited jaw mobility (MIO < 30 mm) and pain (VAS > 2)	11 patients (58%)
Limited jaw mobility only (MIO < 30 mm)	4 patients (21%)
Pain only (VAS > 2)	4 patients (21%)

FFF – free fat flap; MIO – maximal interincisal mouth opening; VAS – visual analog scale

affliction were not included in the cohort, nor were patients with autoimmune or endocrine diseases.

The indication for discectomy with subsequent insertion of FFF (free fat flap) were ongoing difficulties (pain, limitation of jaw mobility) for at least 3–6 months following a preceding arthroscopy. The clinical symptoms before extirpation of the disc were pain and limitation of jaw mobility in 11 patients (58%), limited jaw mobility only in 4 patients (21%), and pain only in 4 patients (21%) (Table 1).

The presence of noise phenomena alone (crepitus) did not constitute an indication for the operation.

Another criterion for indication of discectomy with use of FFF was the presence of only slight changes of joint structure in the sense of flattening of the joint head. Patients where joint head erosions were present, where there were subchondral cysts and changes in the fossa, were dealt with by resection of the joint structures with subsequent reconstruction by total joint replacement.

After the operation the patients underwent regular check-ups at 2 weeks, 1, 3, 6, 12 and 24 months. During examinations there was an assessment of maximum mouth opening (MIO), pain (VAS – visual analog scale 0–10), and presence of noise phenomena and symmetry of mouth opening. For this work there was an evaluation of the results of examinations before the surgery and then 3, 12 and 24 months after the surgery, and the value for mouth opening (MIO – maximal interincisal mouth opening) and pain (VAS) was used for patients where there was no recurrence of the state during the monitored period of 24 months. For all patients undergoing this surgery cone beam computed tomography (CBCT) was carried out before and 24 months after the surgery.

Check-up CBCT was performed for all patients where there was a recurrence of pain and limitation of mobility. In the case of progression of the degenerative changes the state was dealt with by resection of the joint process and subsequent reconstruction of the joint using a custom made total joint replacement (TMJ Concepts, USA).

Performance of surgery

The surgery was performed under general anaesthetic (with nasotracheal intubation). In all cases the endaural approach was selected, then the area of the joint capsule was penetrated via deep subfascial approach and opened with a "T" incision in the lower and upper joint cavity. There followed an eminectomy and disc extirpation including retrodiscal tissue, lavage of joint cavities. Then the free fat flap (FFF) was taken from the umbilical region and inserted in the joint cavity so that it filled it entirely (Figures 1–4). Finally, the wounds were sutured (Machoň, 2017).

Postoperative regime

Postoperative regime consisted of limiting jaw mobility for 3 days, soft foods. From the 4th day after the surgery the patient started to open the mouth again as part of

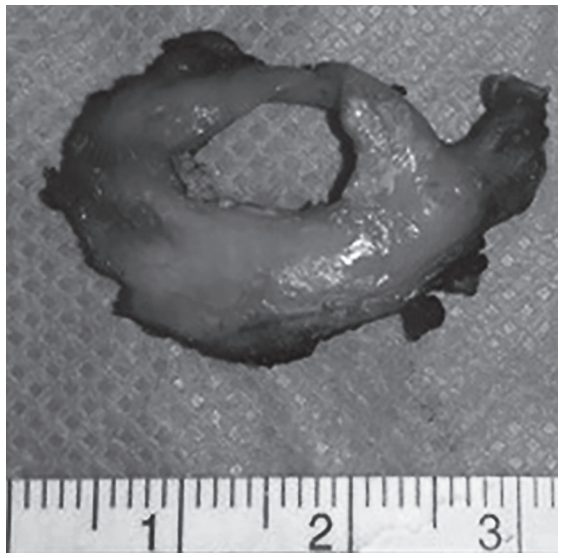

Figure 1 – The perforation of the disc, disc after discectomy.

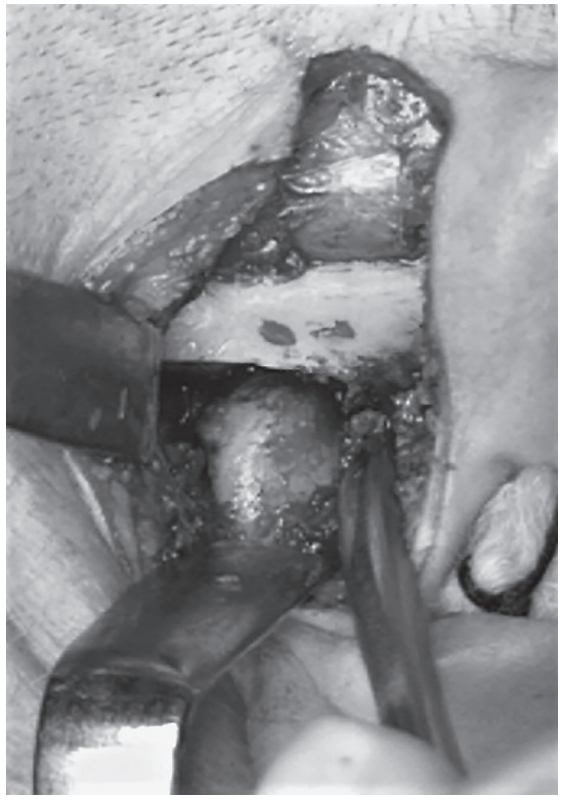

Figure 2 – Temporomandibular joint after discectomy.

Figure 3 – Preparation of free fat flap from the umbilical region.

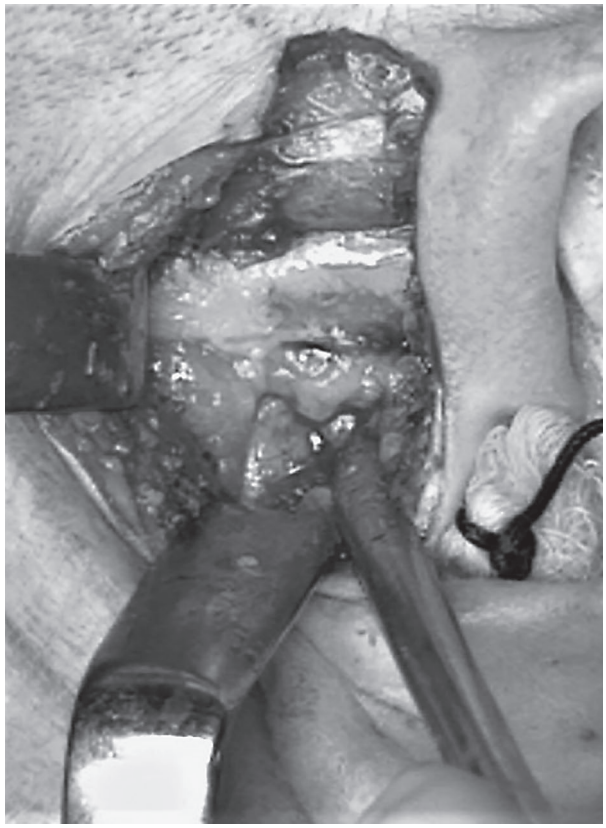

Figure 4 – The joint cavity with free fat flap.

physiotherapy (gradually, up to the pain threshold). An occlusal splint (1.5 mm thick, on lower teeth) was recommended for at least 3 months after the operation, for use 24 hours a day if possible. It was recommended that the occlusal splint be worn regularly at night for 3 months after this.

If hypofunction of the facial nerve was noted during the post-operative period, rehabilitation of the nerve function was initiated immediately on the first day after the operation (Machoň, 2017).

Antibiotics were prescribed for the first week after surgery (Co-Amoxiclav, or for patients who were allergic to penicillin – Clindamycin).

Results

Out of the 19 patients who underwent discectomy with FFF insertion, the operation was ineffective for 3 patients over the monitoring period of 2 years. In 1 patient the difficulties recurred during the first 12 months after the surgery, and in two others 13–24 months after the surgery. In all three patients according to the CBCT there was evident progression in the degenerative changes of joint structures – in all three cases the state was dealt with by a resection of the joint process with subsequent reconstruction of joint.

In the case of patients where there had been no recurrence of the clinical difficulties, 24 months after the operation progression in the flattening of the joint head was observed on the CBCT (in 15 patients), and in 1 case the presence of erosion changes of the joint head.

In 16 patients (84%) the state was stable 24 months after the surgery (opening of mouth more than 30 mm, pain subjectively evaluated at VAS 0–2). In these patients

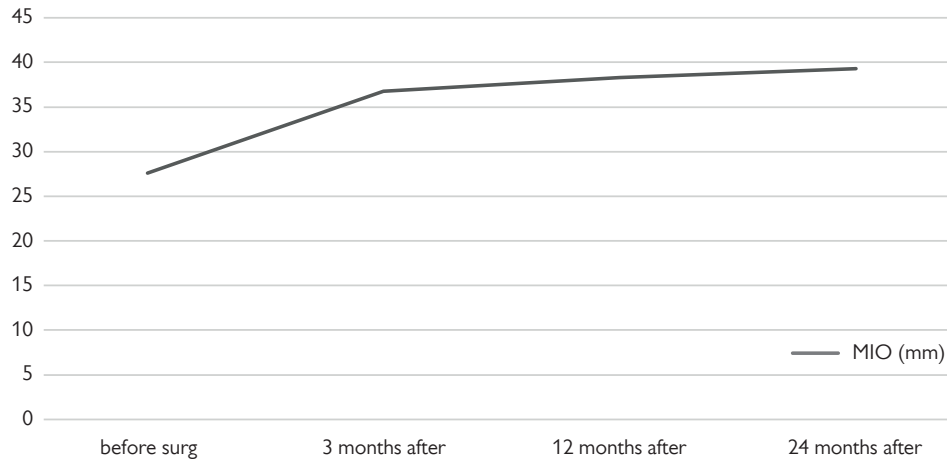

Figure 5 – Evaluation of opening of the mouth in patients where there was no recurrence of the state (16 patients).

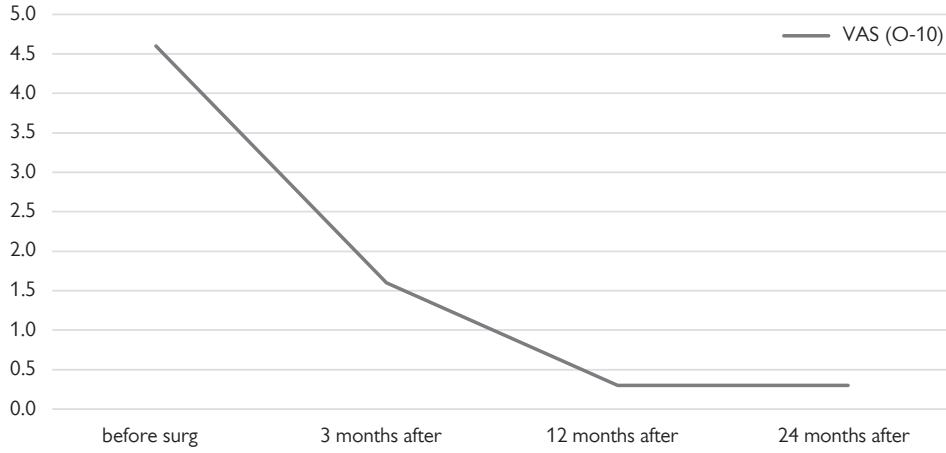

Figure 6 – Evaluation of pain (VAS 0–10) in patients where there was no recurrence of the state (16 patients).

the average value of MIO before the operation was 27.6 mm, 3 months after the operation 36.8 mm, 12 months after the operation 38.3 mm, and 24 months after the operation 39.3 mm (Figure 5).

In all these patients before the operation a deviation had been observed during the opening of the mouth – with deflection of jaw on the afflicted side, 12 and 24 months after the operation symmetrical movement without deviation was achieved in 6 patients (37.5%). In the other patients the movement deviation remained unchanged (10 patients, 62.5%).

The average pain value was given by patients as 4.6 (VAS) before the operation. Three months after the operation the average pain value was 1.6. The average pain value was 0.3 (Figure 6) one and two years after the operation.

In 8 patients (out of 16 patients with effective therapy; 50%), there was a noise phenomenon present before the operation in the form of crepitus, after the operation (3, 12 and 24 months) the noise phenomenon was present in 6 patients (37.5%).

In all cases the operation was performed by a single surgeon, the average operation time was 50 minutes. Post-operative complications were noted in 1 patient (temporary paralysis of ramus temporalis of facial nerve – there was a correction over a period of three weeks following the operation).

In all cases the patients evaluated the healing of scars from the surgical wounds as satisfactory, without complications, in one patient dehiscence of the wound in the umbilical region was observed (but this occurred on the 10th day after surgery, after the patient had fallen).

No other complications were observed.

Discussion

Discectomy is a therapeutic method in patients with disk perforation where preceding therapy (conservation treatment, mini-invasive therapy and arthroscopy) have failed. Persistent pain or mobility block is an indication for a discectomy (Miloro and Henriksen, 2010; Machoň, 2017; Miloro et al., 2017). But the removal of the disc results in direct contact between joint structures and a change of mechanical load (Silver, 1984). This leads to changes in the joint head, in particular to increased sclerotization of the subchondral bones, flattening of the head. Agerberg and Lundberg (1971) described an initial "destructive" phase during the first 6 to 9 months characterized by cortical breakdown. This was followed by a "productive" phase with reconstitution of the cortical surface and expression of altered condylar morphology by 2 years. These morphological changes are not evaluated as progression of degenerative changes, but they represent functional adaptation changes (Silver, 1984; Eriksson and Westesson, 1992; Dimitroulis, 2011). In the work of the authors change in the shape of the joint head were observed over the 2 years following the operation in all patients. In 15 cases progression of flattening of the joint head, in 4 cases erosion – unevenness of the joint head was noted. But clinical symptoms in the sense of post-operative pain and limited mobility were present in only 3 patients – in all cases with unevennesses, erosion of joint head.

Other complications of discectomy are the formation of post-operative adhesions (in cavity created after removal of disc), the formation of ankylotic changes, heterotopic bone formation (Dolwick and Aufdemorte, 1985; Dimitroulis, 2011; Shen et al., 2015). In the 24-month follow-up study the authors did not observe any signs of the formation of heterotopic bone formation, ankylotic changes.

The use of interpositional material between the condyle and cranial base limited the progress of remodelling changes, the formation of adhesions and ankylotic changes (Dolwick and Aufdemorte, 1985). The materials used for disc replacement may be allogenic or autologous (silicone sheets, autogenous dermal graft, dermis-fat graft, auricular cartilage graft, temporoparietal fascia flap, and temporalis myofascial flap, free fat flap) (Dimitroulis, 2011; DeMerle et al., 2017). One question is the ideal interpositional material.

Dimitroulis (2011) presented the criteria for use of interpositional material:

- adequate bulk (fills up the whole joint cavity)
- good handling properties (remains intact during transfer, easy to sculpture during operation, can be easily moulded to fit the entire joint space)
- easy to procure (simple and quick operation; minimal donor morbidity; hidden scar)
- abundantly available (excess tissue available than what is required; can be harvested from multiple sites)
- survives the intra-joint environment (able to adapt to the functional joint demands; does not fragment or degenerate over time)

– facilitates normal joint function (reduces joint noises; permits full range of joint motion; allows pain free joint function)
– prevents bone formation and joint ankylosis (acts as an effective barrier to calcification; eliminates heterotopic bone formation)
– protects condyle from severe remodelling (provides a buffer between the articular surfaces; counteracts the process responsible for condylar degeneration placed)
– long-term safety – data > 2 years available

As evident from the literature, there is no ideal material for disc replacement.

Use of allogenic materials is associated with foreign body reactions, potential cross-infection and unpredictable resorption (Dolwick and Aufdemorte, 1985; Dimitroulis, 2011).

In the case of autologous materials, the 2nd place of collection and thus the aesthetic handicap in the form of a scar is a complication. In the work of the authors the surgical scars in the umbilical region were assessed in 18 cases as satisfactory, in one case there occurred dehiscence of the surgical scar – as a result of the patient falling 10 days after the operation. Other complications of autologous materials are fragmentation of material (when FFF is used), resorption of volume of graft (use of FFF, ear cartilage), epidermoid cyst formation (use of full thickness skin), fibrosis and trismus (use of temporalis muscle), myofascial pain (use of temporalis muscle) (Feinberg and Larsen, 1989; Dimitroulis et al., 2004; Dimitroulis, 2005, 2011; DeMerle et al., 2017).

In the work of the authors there is an evaluation of the use of the free fat flap as interpositional material.

The first description of use of free fat flap as interpositional material is from 1914, where Murphy used it during the treatment of ankylosis (Murphy, 1914). Wolford and Karras (1997) recommend the use of FFF as prevention of heterotopic bone formation and reankylosis in patients who have undergone a total temporomandibular joint replacement. FFF filling the joint cavity or cavity following the resection of joint structures acts as an effective haemostatic in the joint cavity, it prevents adhesions forming (Shen et al., 2015).

The disadvantage of the free fat flap is its fragmentation, which reduces its effect as an interpositional material (Dimitroulis et al., 2004). The fragmentation of the fat flap is reduced by its combination in a joint dermal-fat graft (Dimitroulis et al., 2004; Dimitroulis, 2005, 2011). Another disadvantage of FFF is the reduction in the volume, its resorption. The reduction in the volume of the FFF may be by 1/3 of the original volume during the first year after the operation (Peer, 1950; Kanamori et al., 2001; Dimitroulis, 2011).

Shen et al. (2015) evaluated the reduction in volume of inserted fat on MRI in 267 patients who underwent disc repositioning and where FFF was inserted as prevention against the formation of adhesions. During an examination after

1–3 months the volume of fat had reduced to 57.82%, and after 24 months to 48.44%. Tekin et al. (2014) state the presence of FFF on CT (computed tomography) even 8 years after the insertion of a fat flap, this involved the case histories of patients where unsuitable alloplastic joint replacements were removed. The use of the bucal pedicle flap (BPF) may influence resorption. BPF minimises another disadvantage of FFF – the necessary place of collection, 2nd surgical wound in the umbilical region (Rattan, 2006). Gaba et al. (2012) used BPF as an interpositional material after resection of ankylosis, during a check-up one year after the operation the fat flap was visualised on MRI in 65% of patients.

With regard to the clinical effect of discectomy with subsequent use of FFF: 24 months after the operation 84% of patients (16 patients) had no clinical difficulties (opening of the mouth on average 39.3 mm), pain was evaluated at an average of 0.3. Crepitus was present after 24 months in 37.5% of patients (6 patients). These results correspond with other authors and the use of other interpositional materials (Dimitroulis et al., 2004, 2010; Candirli et al., 2012; DeMerle et al., 2017; Muñoz-Guerra et al., 2018), or the results of patients who underwent only discectomy without replacement (Eriksson and Westesson, 1985; Miloro et al., 2017).

Conclusion

Discectomy with insertion of free fat flap is one possibility for dealing with symptomatic disk perforations where there are also only minimal changes in joint structures. The previous failure of conservative and mini-invasive therapies remains important in the indication criteria.

For the aforementioned criteria the authors find this treatment effective, with a minimum of complications. However, one should take into account the relatively short time of monitoring after the operation (2 years) and limited number of patients in the cohort (19 patients).

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Reversible Cerebral Vasoconstriction Syndrome Associated with a Suprarenal Mass

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Key words: Reversible cerebral vasoconstriction syndrome – Headache – Cerebral angiography – Tumour

Abstract: Reversible cerebral vasoconstriction syndrome (RCVS) is characterised by severe thunderclap headaches (with or without the presence of acute neurological symptoms) and segmental vasoconstriction of cerebral arteries that resolves spontaneously in a period of three months. Cases have been described in the literature with producing and non-producing masses of metanephrines. Within these reports, associations with cavernous haemangioma, medulloblastoma, colon cancer, paraganglioma, pheochromocytoma, uterine fibroids, among others were found. However, no association with adrenal masses which do not produce metanephrines was found. In this context, we reported the case of a woman with this type of tumour associated with RCVS which provided a treatment challenge, as well as we reviewed the literature on cases of RCVS associated with masses.

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Introduction

Reversible cerebral vasoconstriction syndrome (RCVS), or Call-Fleming syndrome, is characterised by severe thunderclap headaches (with or without the presence of acute neurological symptoms) and segmental vasoconstriction of cerebral arteries that resolves spontaneously in a period of three months (Calabrese et al., 2007; Coral and Roa, 2009; Sattar et al., 2010; Yeh et al., 2010; Ducros, 2012; Seby et al., 2015; Ducros and Wolff, 2016). This clinical-radiological entity is characterised by the clinical heterogeneity given by the transitory deregulation of cerebral vascular tone that gives rise to multiple focal points of vasospasm (Sattar et al., 2010; Hongliang et al., 2011).

RCVS has a peak incidence around the age of 42 and is more common in women than in men (Chen et al., 2010; Ducros et al, 2010; Ducros, 2012). It is usually self-limited and has a low incidence of recurrence (Sattar et al., 2010). The main complications of this syndrome are ischaemic and haemorrhagic strokes (Ducros et al., 2010; Sattar et al., 2010). Moreover, approximately 60% of the cases are secondary to a probable cause; the most common being the postpartum period or after exposure to vasoactive substances (Sattar et al., 2010; Ducros, 2012). Because of its multifactorial origin, this syndrome represents a diagnostic challenge. Nevertheless, a high diagnostic suspicion is fundamental to achieve timely management.

Cases have been described in the literature with producing and non-producing masses of metanephrines (Mori et al., 2012; Duke and Ullrich, 2018; Katada et al., 2018; Arenas-Beltrán et al., 2019). Within these reports, associations with cavernous haemangioma, medulloblastoma, colon cancer, paraganglioma, pheochromocytoma, uterine fibroids, among others were found (Mori et al., 2012; Duke et al., 2018; Katada et al., 2018; Arenas-Beltrán et al., 2019). However, no association with adrenal masses which do not produce metanephrines was found. In this context, we reported the case of a woman with this type of tumour associated with RCVS which provided a treatment challenge, as well as we reviewed the literature on cases of RCVS associated with masses.

Case report

A 55-year-old female original from a rural area Colombia, presented with acute onset frontoparietal left headache which the patient described as the sudden most intense pain she has ever felt in her life. Pain was not associated with changing positions and was not relieved by NSAIDs or paracetamol. Associated with the headache, she described left periocular pain, phonophobia, photophobia, tinnitus, nausea and emesis. She also pointed out that she had been presenting at least 5 episodes of this headache per week during the last month. Each episode reached the highest intensity of pain before 1 minute and lasted for around one hour. She experienced the last episode 6 hours prior the consultation, where she additionally referred blurred vision by both eyes.

She had history of headaches since she was 25 years old with the same localization, however those episodes were much milder, with a much insidious onset and where relieved with NSAIDs or paracetamol. Additionally, she had history of type 2 diabetes, arterial hypertension, intradermic melanocytic nevus and a basocelular carcinoma infiltrating the deep dermis.

At the initial examination, her blood pressure was 160/90 mm Hg and the rest of the vitals were normal. Visual acuity bilaterally was restricted to light perception, however fundoscopy was normal on both eyes. Additionally, she presented hypoesthesia on the superior right limb and right agraphesthesia. Rest of the exam was normal.

Magnetic resonance imaging (MRI) was performed finding left occipital and parietal hyperintensities which did not restrict on the diffusion and enhanced with the injection of contrast. These were interpreted as haemorrhagic transformations with mild subarachnoid bleeding. Angiography was then performed finding multiple focal and diffuse stenosis on the anterior and posterior circulation with pre-occlusive arteries on the left parietooccipital territory which conditioned delayed flow bilateral occipital lobes. These findings were interpreted as intracranial vasculitis. Therefore, autoimmune panel and lumbar puncture were performed without any abnormal findings. Based on this, a diagnosis of reversible cerebral vasoconstriction syndrome was made and nimodipine 60 mg 3 times daily was prescribed.

Despite the treatment, she kept presenting around 3 episodes of headache per day. Transcranial Doppler was negative for vasospasm, however the median cerebral arteries (MCA) were found to have higher resistance index. Because of this and the persistent visual acuity decrease, intraarterial nimodipine application through angiography was prescribed. During this angiography, a worsening of the stenosis on the anterior bilateral circulation was seen. Nimodipine was intraarterially administered (6 mg on the left hemisphere and 4 mg on the right one) with an improvement of the calibre of both MCAs. On the aetiology studies, an abdominal CT (computed tomography) reported a left suprarenal lesion suggestive of adenoma.

She was asymptomatic after the intra-arterial nimodipine injection. Still, one week after, she refers again thunderclap headache associated with left superior limb weakness and paraesthesias. Because of this, a new therapeutic and angiography was made. Intra-arterial nimodipine was administered (7 mg on the left hemisphere and 2 mg on the right hemisphere) without a complete reopening of the MCAs, yet the symptoms resolved. The next day, she referred a new thunderclap headache and weakness and paraesthesias on her right superior limb. A fourth angiography was indicated where it was documented opercular and cortical refractory vasospasm on the left MCA (Figure 1). Nimodipine was administrated intraarterially, however an unfavourable evolution was documented with multiple arterial stenosis due to vasoreactivity. Suddenly, she presented disorientation, anterior aphasia, right hemi-inattention, weakness on her right inferior limb and right hemisensitve syndrome

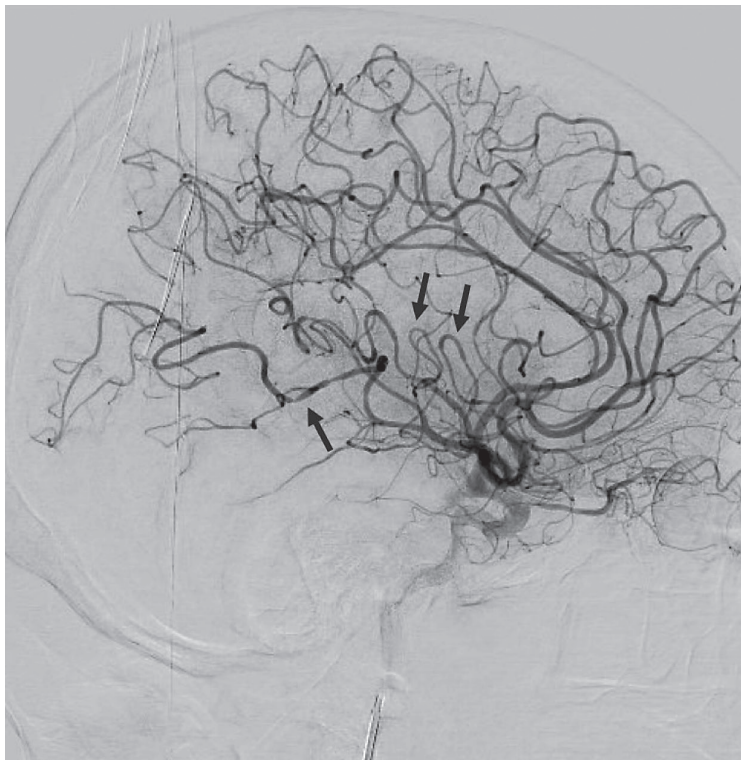

Figure 1 – Angiography showing narrowing of the arteries corresponding to vasospasm.

associated. Arterial stenosis on the left frontal, parietal and parietooccipital territories was documented with unresponsive changes to milrinone and nimodipine. Because of the intense pain she was feeling, 25 mcg of phentanyl and 1 mg of midazolam where administrated and the procedure was stopped. Patient was translated to the intermediate care unit and systemic intraarterial nimodipine was started at a 10 mg/hour dose with resolution of the symptoms.

Two days after, she referred a thunderclap headache with right hemiparesis associated with a thunderclap headache. A sixth angiography was made and this time, the left parietooccipital region was found to be permeable again however the defect at the left parenchimogram was still present. Intraarterial nimodipine was again started with poor angiographical response, yet with good clinical response. By the end of the procedure, systemic arterial pressure decreased, and noradrenaline had to be started. Nimodipine was changed from i.v. administration to the oral form 30 mg every six hours. She was translated to the intensive care unit where she was observed for 5 days with resolution of the headache and with adequate blood pressure control.

After 10 days of the last thunderclap headache episode and after 7 days of the last angiography, patient was dismissed with a persistent right hemiparesis. Ambulatory PET scan was programmed for the study of the suprarenal lesion and oral nimodipine was continued. She was seen two weeks after being dismissed on the external neurology clinic with no new thunderclap headaches episodes and with partial resolution of the right hemiparesis.

Discussion

This case illustrates the classic clinical presentation of RCVS. Thunderclap headache is usually the typical symptom with or without neurological focalization and the diagnostic criteria suggested by Calabrese et al. (2007) propose that headache should be associated with diffuse changes in the tone of the cerebral vasculature documented by angiography (De Angelis et al., 2018; Arenas-Beltrán et al., 2019). Because it is usually associated with medical conditions, a classification dividing the aetiology of the syndrome between idiopathic and symptomatic has been purposed (Coral and Roa, 2009). When the RCVS is considered to be symptomatic, pregnancy, neoplasms and systemic diseases should be considered as the primary disease (Coral and Roa, 2009). Because of this relationship, in the clinical setting it becomes necessary to study the patient looking for an underlying aetiology that triggers the multifocal and diffuse cerebral vasospasm (Coral and Roa, 2009). In the presented case, an abdominal CT scan documented a left adrenal lesion suggestive of adenoma as the only abnormal finding.

Adrenal masses are usually found as an incidental finding (incidentalomas) in 0.4% of all the abdominal CT scans (Herrera et al., 1991). Malignancy is uncommon in patients without a known cancer diagnosis and it can be predicted by the size of the mass, nevertheless, size and imaging characteristics may help determine whether the tumour is or not cancer (Cawood et al., 2009; Nieman, 2010). It has been reported that masses bigger than 4 cm are associated with adrenocortical carcinoma (Herrera et al., 1991). Concerning the imaging phenotype, a consensus panel reported that a homogenous adrenal mass with a smooth border and an attenuation value < 10 HU on a simple CT is very likely to be benign, different from pheochromocytomas which usually increase attenuation > 20 HU on the CT and show increased mass vascularity with delay in the contrast medium washout or the adrenocortical carcinoma which are usually irregular, have usually a diameter greater than 4 cm and present non homogeneous density due to tumour necrosis or calcifications (Grumbach et al., 2003).

There are some cases describing the association between the appearance of tumours and RCVS (Mathis et al., 2017; Arenas-Beltrán et al., 2019). Paragangliomas are the most frequent association that has been reported (Arenas-Beltrán et al., 2019). Although there is a clear physiopathological association between tumours producing vasoactive agents, the most frequently reported cases are of non-secretory tumours ass less than 5% of the paragangliomas secrete catecholamines (Mathis et al., 2017) paraganglioma may affect the carotid body (carotid body

tumour. As sixty percent of head and neck paranganglioma are carotid body tumours, situated at the bifurcation of the common carotid artery, it is accepted that they can compromise the baroreceptor reflex triggering trigger hypertension, headache and tachycardia (Mathis et al., 2017; Arenas-Beltrán et al., 2019).

By the time of the reporting of this case, there have been no cases of RCVS associated with suprarenal adenoma published. Although tumours may favour the appearance of RCVS, it has also been described that surgical and non-surgical oncologic treatment may induce vascular changes at the brain level that lead to the disease (Mathis et al., 2017; Duke et al., 2018; Katada et al., 2018). In the case of radiotherapy, particularly in brain tumours, it can lead to dynamic vascular lesions and generate pathologies such as RCVS, SMART syndrome (stroke-like migraine attacks after radiation therapy), Moya-Moya disease or even haemorrhagic cerebrovascular attack (Duke et al., 2018; Katada et al., 2018). Similarly, there is an association between treatment with chemotherapy and the appearance of vasospasm at the cerebral level, as is the case of the chemotherapy regimen with oxaliplatin and capecitabine, which has been linked as an aetiology of subsequent reversible leukoencephalopathy syndrome presented with RCVS in up to 38% of cases (Mathis et al., 2017; Duke et al., 2018; Katada et al., 2018).

Given that RCVS is a clinical-radiological, multifactorial, low incidence and difficult to diagnose entity, there is not enough evidence to provide a precise physiopathological explanation which associates non-functional tumours with the disease, to such an extent that some authors exclude the presence of tumours in the risk factors for developing multifocal and segmental vasospasm at the cerebral level (Robert et al., 2013, de Boysson et al., 2018). Nevertheless, there are multiple published cases that relate both the presence of tumours with RCVS, so oncologic pathologies, even after receiving treatment either surgical, chemotherapy, radiotherapy or endovascular, should be considered as a risk factor to reduce the rate of underdiagnosis and identify new conditions that generate the disease (Mori et al., 2012; Robert et al., 2013; de Boysson et al., 2018).

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Life Threatening Delayed Complication of Botulinum Toxin Injection for Treatment of Spasmodic Dysphonia

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Key words: Dysphonia – Botulinum toxin – Vocal cords

Abstract: Spasmodic dysphonia is a primary task specific focal dystonia affecting the laryngeal muscles during speech. Most medical and surgical approaches to treatment of spasmodic dysphonia are aimed at the denervation of the laryngeal muscles to block symptom expression in the voice. The standard of care for the adductor form of spasmodic dysphonia is botulinum toxin chemodenervation. The common side effects of treatment with Botox are excessive breathiness and aspiration of fluids. We present the report of a delayed presentation of upper airway obstruction due to a complete vocal cords adduction requiring intubation ten days post Botox injection for the adductor form of spasmodic dysphonia. This presentation may be preceded by a change in voice, productive cough, shortness of breath, or odynophagia. We would recommend supportive treatment in an Intensive Care Unit and close liaison with the otolaryngology team for the management of this complication. Acute upper airway obstruction requiring tracheal intubation is a delayed complication of botulinum toxin administration in the adductor form of spasmodic dysphonia.

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Introduction

Spasmodic dysphonia (SD) is a primary task specific focal dystonia affecting the laryngeal muscles during speech (Ludlow, 2009). There are three classic types of SD: adductor spasmodic dysphonia (ADSD), abductor spasmodic dysphonia, and mixed spasmodic dysphonia. ADSD is the most common form (Simpson et al, 2016). The diagnosis is based on a careful history and examination of the glottis during a variety of laryngeal tasks (Sulica and Blitzer, 2004).

Most medical and surgical approaches to treatment of SD are aimed at the denervation of the laryngeal muscles to block symptom expression in the voice (Ludlow, 2009). The standard of care for ADSD is botulinum toxin (Botox) chemodenervation (Stachler et al., 2018). The common side effects of treatment with Botox are excessive breathiness and aspiration of fluids (Blitzer et al., 2018).

We describe a case of acute upper airway obstruction due to complete vocal cords adduction requiring intubation ten days post Botox injection for ADSD.

Case report

We present a case of a 64-year-old lady with the background of ADSD, seronegative rheumatoid arthritis, osteoarthritis and hypothyroidism.

She had been treated with triennial Botox injections for ADSD for three years. She was noted to develop mild stridor after previous two injections, but underwent a third injection. On day six, she noticed a change in voice, productive cough, shortness of breath and odynophagia. On day eight, she visited her general practitioner, who prescribed Amoxicillin for presumed respiratory infection.

She presented to the Emergency Department of a District General Hospital (without inpatient otolaryngology services) with acute stridor on day ten post injection. She was initially treated with 10 mg of nebulised adrenaline and 200 mg of intravenous hydrocortisone. Flexible nasendoscopy (FNE) was performed and showed completely adducted vocal cords with very limited motility. She underwent emergency tracheal intubation by an intensive care consultant and was transferred to the Intensive Care Unit (ICU) for ventilation.

On ICU, patient was prescribed her regular medication, proton pump inhibitor, enoxaparin, and subglottic levobupivacaine. She received nasogastric feeding. She required minimal ventilatory support on CPAP ASB with PEEP of 5 and FiO_2 0.3–0.35. She tolerated endotracheal intubation with propofol and remifentanil sedation aiming RASS –1 to 0.

On day five of ICU admission, she was started on Co-Amoxiclav 1.2 g three times a day for ventilator associated pneumonia. A trial extubation on day six was unsuccessful. FNE showed minimal movement and oedema of vocal cords.

A further trial of extubation was attempted on day eight of ICU admission. She was successfully extubated to face mask CPAP.

Following assessment by physiotherapists and swallow and language therapists, patient was deemed medically fit for discharge. She was discharged home on day twelve.

Discussion

Different treatment options for SD are described in the literature. The vast majority are aimed at the denervation of laryngeal muscles (Ludlow, 2009).

Dedo described the recurrent laryngeal nerve (RLN) section as the treatment for ADSD in 1976. The subsequent change in voice was treated with speech therapy (Dedo, 1976). Fritzell et al. (1993) reported that this treatment had 72% recurrence rate at ten years follow-up due to the reinnervation of the RLN. Bilateral selective division of the adductor branches of the recurrent laryngeal nerves with immediate reinnervation of the distal nerve trunks with branches of the ansa cervicalis (selective denervation-reinnervation) was reported by Allegretto et al. (2003). Other surgical approaches include RLN avulsion (Nettervillee et al., 1991), laser-assisted thyroarytenoid myomectomy (Woo, 1990), and laryngeal framework surgery (Tucker, 1989).

Despite multiple available options of surgical treatment, the standard of care for ADSD remains botulinum toxin chemodenervation (Sulica, 2004; Stachler et al., 2018). The clinical effects of Botox last approximately 3 to 4 months on average, and reinjection is typically required to maintain clinical benefits. The broad success of Botox may be due to the specificity, repeatability, and reversibility of the chemodenervation (Blitzer et al., 2018). Patients undergoing long-term botulinum toxin treatment report a positive effect of this treatment in their workplace (Meyer et al., 2013).

Unwanted effects of Botox therapy may include loss of muscular volume and breathiness of voice (Simpson et al., 2016). Blitzer et al. (2018) described the following side effects of Botox injection in the ADSD population: mild breathiness on speaking, mild difficulty drinking fluids, and local pain, itching, or rash. The breathiness and dysphagia to liquids were also observed by Novakovic et al. (2011). A unilateral true vocal cord paralysis was reported (Srirompotong et al., 2006).

Venkatesan et al. (2010) described bilateral abductor paralysis (BAP) as a complication of Botox administration. Retrospective analysis of 352 patients over the period of 9 years showed that 8 patients developed BAP between 1 week and 1 month post injection. Notably, all affected patients were female over the age of 50 years. The complication was attributed to the diffusion of Botox to the posterior cricoarytenoids. None of the patients were reported to require intubation; however, in one case a temporary tracheostomy was inserted (Venkatesan et al., 2010).

We present the report of a delayed presentation of upper airway obstruction post botulinum toxin administration for ADSD. This presentation may be preceded by a change in voice, productive cough, shortness of breath, or odynophagia. We would

recommend supportive treatment in ICU and close liaison with the ENT team for the management of this complication.

Conclusion

Acute upper airway obstruction requiring tracheal intubation is a delayed complication of botulinum toxin administration in ADSD.

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Dengue Infection: A Hidden Cause of Acute Insult in a Case of Acute on Chronic Liver Failure in Endemic Area

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Key words: ACLF – Dengue infection – Endemic area – Acute insult – Precipitating factor

Abstract: Acute on chronic liver failure (ACLF) can be precipitated by several factors such as bacterial infection, alcohol intake, viral hepatitis, surgery, etc. Identification of precipitating factor is an important part of management of ACLF. A middle aged gentleman was presented with features of acute liver failure and after through history and investigations, he was diagnosed as acute on chronic liver failure. Chronic liver disease was first diagnosed after this event of acute insult. Precipitating factor of ACLF was dengue fever in this case report. Therefore, in endemic area of dengue infection, dengue serology tests which are not routinely done should be advised to identify dengue infection as an acute insult in ACLF.

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Case report

Fifty-year-old non-diabetic, non-hypertensive gentleman, who was on alcohol (more than three standard drinks per day) for last 15 years, was admitted with fever, abdominal distension, and jaundice for 10 days duration, and altered sensorium for last 3 days duration. He had no history of any herbal medication or binge of alcohol intake before onset of jaundice and also he did not have any history of melena or haematemesis during or before this event. On admission, he was hemodynamically stable but disoriented. Pulse rate and blood pressure were 116/min and 110/82 mm Hg respectively. On physical examination, he had anaemia, jaundice, pedal edema, fever and grade III hepatic encephalopathy but no palmar erythema, spider nevi (angiomata), gynaecomastia. On abdominal examination, he had free fluid in abdomen, and respiratory system and cardiovascular system were normal. Initially he was treated in local hospital and then referred to our hospital for further evaluation and management.

After taking history and physical examinations, provisional diagnoses were acute liver failure (ALF) (in view of jaundice followed by ascites and grade III hepatic encephalopathy within ten days of onset of jaundice), acute on chronic liver failure (ACLF) (suspected aetiology of chronic liver disease was alcohol, and suspected

Table 1 – Blood investigation at the time of admission and during discharge

Investigations	Test value at the time of admission	Laboratory value at the time of follow-up visit
Haemoglobin	8.9 g/dl	10.6 g/dl
White blood cell (WBC) count	9,000/cu mm	7,000/cu mm
Platelet count	128,000/cu mm	152,000/cu mm
Prothrombin time	25.8 s	18.7 s
Mean normal prothrombin time	12.3 s	12.3 s
International normalized ratio	2.16	1.55
Total bilirubin	10.5 mg/dl	3 g/dl
Direct bilirubin	5.3 mg/dl	1.2 g/dl
Aspartate aminotransferase	94 U/l	72 U/l
Alanine aminotransferase	99 U/l	46 U/l
Albumin	2.3 g/dl	2.7 g/dl
Creatinine	1.63 mg/dl	0.92 mg/dl
Sodium	133 mmol/l	136 mmol/l
Potassium	2.9 mmol/l	3.7 mmol/l
Ammonia	197 µmol/l	not done
Procalcitonin	<0.10 ng/ml	not done
C-reactive protein (CRP)	26.4 mg/l	9.5 mg/l
Blood smear for malaria parasite	not found	not done
Glycosylated (HbA1c)	5.6%	not done
pH(Arterial blood gas analysis)	7.423	not done
Lactate	2 mmol/l	not done

acute insult was infection and/or alcohol) and acute severe alcoholic hepatitis (in view of alcohol intake for last 15 years).

On the day of admission, laboratory examinations of blood (Table 1) showed: total leukocyte count 9,000/cu mm, hemoglobin 8.9 g/dl, platelet count 128,000/cu mm, mean corpuscular volume 114.8 fl, creatinine 1.63 mg/dl, Na^+ 133 mmol/l, K^+ 2.9 mmol/l, procalcitonin < 0.10 ng/dl, arterial ammonia 197 µmol/l, prothrombin time 25.8 s (control: 12.3 s), and international normalized ratio (INR) 2.16.

His liver function test (LFT) showed following abnormalities: total bilirubin 10.5 mg/dl, aspartate aminotransferase (AST) 94 U/l, analine aminotransferase (ALT) 53 U/l, albumin 2.3 g/dl, alkaline phosphatise (ALP) 99 U/l. Blood, urine and ascitic fluid culture showed no growth. Chest X-ray (PA – posteroanterior view) and echocardiography were normal. HBsAg, IgM anti HBc, total anti HBc, anti HCV, anti HAV IgM and anti HEV IgM were non-reactive (Table 2). At the time of hospital admission his MELD score and CTP score were 29 and 13 respectively (Table 3).

Contrast enhanced computed tomography of brain was done in view of altered sensorium and showed no abnormality but ultrasonography (USG) abdomen identified following abnormalities: course echotexture of liver, splenomegaly and moderate ascites.

Table 2 – Serology tests at the time of admission

Tests	Result
Anti HAV IgM	non-reactive
Anti HEV IgM	non-reactive
HBsAg	non-reactive
IgM anti HBc	non-reactive
Total anti HBc	non-reactive
Anti HCV antibody	non-reactive
Dengue IgM antibody	reactive
NS1 antigen test	positive
Malaria antigen test	negative

HAV – hepatitis A virus; HEV – hepatitis E virus; HBsAg – hepatitis B surface antigen; HCV – hepatitis C virus

Table 3 – Different scoring system at the time of admission

Score	Value
MELD score	29
$MELD_{Na}$ score	30
Child-Pugh-Turcotte score	13 (class C)
APASL ACLF research consortium (AARC) score	11

APASL – Asian Pacific Association for the Study of the Liver; MELD – Model for End-stage Liver Disease

Stool was sent for occult blood test in view of anaemia and revealed positive result. Stool culture was not done because he did not have any history of loose stool. Upper GI (gastrointestinal) endoscopy showed grade II oesophageal varices but no active bleeding or presence of any red colour sing, mild portal hypertensive gastropathy without red spots, and no gastric varix.

After abdominal USG and upper GI endoscopy, acute liver failure was excluded from provisional diagnosis. Initially we thought it was a case of acute on chronic liver failure (ACLF) (aetiology of CLD – chronic liver disease – was alcohol; acute insult was alcohol intake in view of no bacterial growth in blood, urine and ascitic fluid culture and normal blood procalcitonin value).

Dengue serology was advised in view of dengue outbreak in our area (dengue endemic area) and report showed that dengue IgM antibody and NS1 antigen were positive. After this blood report our final diagnosis was ACLF (aetiology of CLD was alcohol and acute insult was dengue infection).

He was treated conservatively and improved symptomatically. Twenty-two days after admission, he was discharged in stable condition and advised to come for follow-up after 2 weeks from the date of discharge.

Discussion

ACLF definition was first proposed by Asian Pacific Association for the Study of the Liver (APASL) in 2009 and again modified in 2014. According to APASAL (2014), "ACLF is an acute hepatic insult manifesting as jaundice (serum bilirubin ≥ 5 mg/dl (85 micromol/l) and coagulopathy (INR ≥ 1.5 or prothrombin activity < 40%) which is complicated within 4 weeks by clinical ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease/cirrhosis, and is associated with a high 28-day mortality" (Sarin et al., 2014). According to World Gastroenterology Organization (WGO), "ACLF is a syndrome in patients with CLD with or without previously diagnosed cirrhosis characterized by acute hepatic decompensation resulting in liver failure (jaundice and prolongation of the international normalized ratio), and one or more extra hepatic organ failures, that is associated with increased risk for mortality within a period of 28 days and up to 3 months from onset" (Jalan et al., 2014). In our case, patient was suffering from chronic liver disease which was undiagnosed before incidence of acute insult. Aetiology of CLD was alcohol intake, and acute insult was dengue infection. Our case was diagnosed as acute on chronic liver failure by following the APASL diagnostic criteria of ACLF.

ACLF management needs treatment of underlying precipitating factor, organ failure support and other supportive care. Treatment plan depends on MELD score; when MELD score < 30, ACLF is treated by supportive care but if MELD score ≥ 30, patient should be sent for urgent liver transplantation evaluation (Sarin et al., 2014; Sarin and Choudhury, 2016). Organ failure is not a contraindication for transplantation, except when patient needs cardiac or pulmonary support or has rapidly progressing organ failure at day four or seven (Sarin et al., 2014).

APASL ACLF research consortium (AARC) score of ACLF (based on MELD and lactate) is highly specific and sensitive to assess prognosis and has better predictive value than MELD or CLIF-SOFA score (Sarin et al., 2014). ACLF grade (based on CANONIC study) predicts mortality and patients with grade 3 ACLF show the poor prognosis compared with ACLF grade 1 and 2 (Moreau et al., 2013). Chronic Liver Failure Consortium ACLF score (CLIF-C ACLF score) showed a significantly higher predictive accuracy than MELD, MELD-Na and Child-Pugh-Turcotte score after ACLF diagnosis. Number of organ failure is also a predictor of morbidity and mortality in ACLF.

Liver enzymes are elevated in 30% of the cases of dengue fever (Lee et al., 2012). Dengue related acute liver failure has been described in few case reports and majority of them are reported in children and young age group (Subramanian et al., 2005). Cirrhotic patients usually do not have classical features of dengue and associated with poor prognosis. Dengue should be suspected as a cause of liver failure in endemic areas where no precipitating factor is identified (Kulkarni et al., 2019). Therefore, in endemic areas, dengue can cause acute insult on chronic liver disease resulting in ACLF. In our study, dengue was responsible for worsening of chronic liver disease.

Conclusion

Dengue infection is commonly presented with uncomplicated dengue fever. Dengue infection can cause asymptomatic elevation of liver enzymes and rarely acute liver failure. Like other hepatic complications, dengue infection can be responsible for acute insult on chronic liver failure leading to ACLF. So in dengue endemic area if patient is presented with acute hepatic decompensation or ACLF, dengue serology test should be done along with other investigations to rule out dengue infection as an acute insult.

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