Editorial Note

A concerted effort combating hepatitis

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ARTICLE INFO

Article history:
Received 1 October 2022
Accepted 3 October 2022
Available online 7 October 2022

Keywords:
Hepatitis
Ovarian cancer
Mitochondria
Organ transplant

ABSTRACT

In this issue of the Biomedical Journal one focus is the research of hepatitis. The reader learns about the connection between hepatitis and thrombocytopenia and a large-scale immunization initiative against hepatitis. Further articles include an overview of mitochondrial bioenergetics, a review of current methods to research neuronal dynamics, a study of the anti-cancer effect of propolis, and the challenges of organ transplants derived from brain dead donors. An insight into kidney disease and types of stroke is provided, as well as imaging techniques that are employed for identifying changes in white matter. Lastly this issue contains the results of a study investigating foot arch development in children, the use of a precision radiation therapy against head and neck carcinoma, and an exchange concerning renal impairment and serum cancer antigen-125.

Spotlight

On the recent World Hepatitis Day in July 2022, the WHO raised concerns about the new outbreak of unexplained acute hepatitis infections affecting children worldwide.1 There are seven types of hepatitis, five of which are of viral origin: hepatitis A, B, C, D and E.2 Hepatitis A is mostly a food-borne illness, hepatitis B is transmitted through exposure to contaminated blood, needles, bodily fluids and from mother to baby. Type C is only transmitted through infected blood or from mother to newborn during childbirth. Hepatitis D is exclusively found in people already infected with type B.3 Type E transmission occurs largely via the fecal-oral route [1].

Viral hepatitis entails inflammation of the liver, potentially progressing to fibrosis, cirrhosis or liver cancer. In particular type B and C lead to chronic disease in alarming numbers worldwide. Currently hepatitis type A, B, and D are preventable by immunization.4

The WHO set a target to achieve elimination of hepatitis by 2030 through measures like the reduction of new infections of hepatitis B and C by 90%.5

Hepatitis C virus (HCV) infection has been associated with immune thrombocytopenia, possible mechanisms causing immune destruction include the cross-reaction of antibodies and suppression of bone marrow production by HCV [2]. In this issue of the Biomedical Journal, Huang et al. present a retrospective study, taking a closer look at the impact of...
different risk factors for HCV-associated thrombocytopenia (HCV-TP) and hepatitis B virus-associated thrombocytopenia (HBV-TP). The results show that predictive risk factors for thrombocytopenia vary depending on viral type and thrombocytopenia severity. HCV patients showed a higher cross-sectional prevalence and longitudinal follow-up incidence rates of thrombocytopenia than HBV patients [3].

A mass initiative against hepatitis

Hepatitis B virus (HBV) integrates its DNA into the host nucleus as covalently closed circular DNA (cccDNA) that can persist indefinitely in the hepatocytes. This ability accounts for the possibility of HBV reactivation in chronic, inactive disease. The virus DNA inter alia expresses two core proteins, hepatitis B antigen e (HBeAg) and hepatitis B surface antigen (HBsAg). The first phase in chronic HBV infection is termed immune tolerant and characterized by elevated HBV titers and positive HBeAg. During the acute infection phase, HBsAg becomes positive and can thus support acute HBV diagnosis [1].

In 1984 Taiwan launched a mass immunoprophylaxis program to combat HBV infection with the first goal to prevent chronic perinatal HBV carriage from mother to infant. Following the program guidelines infants to HBSAg-positive women were given a hepatitis B (HB) vaccine, and infants of highly infectious carrier mothers additionally received HB immune globulin within 24 h after birth [4,5]. The program is still in place and has been further fine-tuned over the years. The initiative is deemed to be successful as studies over more than three decades have observed. Results include a decrease in seroprevalence of HBsAg in children, a decline in mortality from fulminant hepatitis as well as hepatocellular carcinoma in children. Furthermore the program has been extended to the entire population, and an antiviral therapy program against hepatitis B and C was introduced, leading to a substantial reduction in end-stage liver disease [6–9]. [see Fig. 1].

However, HB vaccine failure in children born to HBeAg-positive mothers and overall breakthrough HBV infection rates among infants have also been reported. The reader can read up on a study of Wu et al. in this journal issue, where the success rate of the HB vaccination program among high-risk children in Taiwan is evaluated. The research team found that even after vaccination 44% of children showed HBV infection [10]. One major factor contributing to mother-to-child transmission despite immunoprophylaxis is suggested to be the maternal viraemia. Vertical transmission of HBV during childbirth is considered a major reservoir for chronic infection globally. Maternal screening in combination with passive and active immunoprophylaxis at birth and, if indicated, complementary administration of antiviral treatment are key in the strategic approach to eliminating HBV infection [11]. Wu et al. also suggest that delivery by C-section might be a feasible mean to reduce vertical transmission in mothers receiving antiviral treatment [10].
deformity for his ill reputation. In the 1500s, physical appearance was believed to be an indicator of personality. The portrayal of Richard III having severe scoliosis probably kindled spreading of rumors that he was of evil character. The skeleton could only be identified thanks to comparison of its mitochondrial DNA with that of two matrilineal descendants of the sister of King Richard III [12].

The mitochondrial genome harbors some interesting features besides matrilineal inheritance. The genome has about a 100-fold higher mutation rate than the nuclear genome, and mitochondrial DNA involvement in diseases may especially manifest in tissues with high energy demands such as brain, retina, skeletal and cardiac muscle tissue [13].

Bhatti et al. provide the reader with a review of the current literature on mitochondrial bioenergetics in different conditions, and therapeutic potential of compounds targeting mitochondria in metabolic and neurodegenerative diseases [14].

Deep dive into grey and white matter
Anjul Khadria dives into the depths of current tools employed to further our understanding of the brain and associated diseases. The author discusses in his review the working principles, benefits as well as challenges of classical electrode-based techniques and optical imaging-based methods. He considers that an ideal technique should allow measuring the potential of a large number of neurons at high resolution for long time in deep tissues without loss of efficiency or perturbation of neuronal dynamics. The author is confident that the currently increasing and diversified research approaches will soon open the path to completely understand the human brain [15].

Original articles
Ad fontes — back to the sources
Beekeeping can be traced back to 13,000 BC and bee products have been extensively used by ancient Greeks, Romans, Egyptians, and Persians. One of those products is the wax-like substance propolis that bees apply as defensive coating on the inner walls of a beehive. In ancient medicine, propolis was known for its healing properties, but lost popularity in the middle ages [16,17]. The interest in traditional folk medicine in Europe returned with the concept Ad fontes. The term was coined by the Christian Renaissance humanist Erasmus, and emphasized the importance of studying original sources and documents in the original languages. Within this context propolis was also rediscovered for its therapeutic benefits [17].

Nowadays it has been shown that the bioactive component caffeic acid phenethyl ester (CAPE) found in propolis exerts pluripotent activities including anti-viral, anti-bacterial, anti-cancer, immunomodulatory, and wound-healing effects [18].

Hou et al. evaluated the anti-cancer effect of CAPE on bladder carcinoma cells in vitro and in a xenograft mouse model. The team found that CAPE induced expression of GDF15 as well as the expression of downstream genes NDGR1 and maspin in a dose-dependent manner. GDF15 knockdown showed attenuation of the anti-proliferation and anti-invasion effects of CAPE. CAPE furthermore inhibits tumor growth in vivo, involving the ERK, p38 or AMPKα1/2 signaling pathway. CAPE therefore presents as promising preventive agent against the growth of human bladder carcinoma cells [19].

Organ donations after brain death
Transplantation of organs, tissues or cells is nowadays frequently the only life-saving therapy for a number of serious and life-threatening diseases or conditions. A steady rise in end-stage diseases for instance keeps the demand for organ transplantations high, outpacing organ availability. Organs provided for transplantation after neurological death constitute the majority of donations. Additionally, those donations are among other things the only source of thoracic organs suitable for transplantation. However, organs from brain-dead donor patients may be severely affected in both quantity and quality due to the pathophysiological changes accompanied by brain stem death [20].

Walweel et al. investigated in sheep the pro-inflammatory cytokine profiles as well as cardiovascular physiology over the duration of 6 h after brain stem death (BSD) induction. Following BSD the team observed an early systemic and lung inflammatory response, characterized by increased neutrophil infiltration, increased cytokine production, and furthermore reduced heart contractile function. Walweel et al. suggest that these changes could lead to graft dysfunction in the donor organ [21]. Current approaches to improving organ viability take into account organs previously infected with hepatitis C, that can be treated before transplantation. Another strategy comprises normothermic organ preservation where organs to be transplanted are pumped with warm and oxygenated blood for prolonged preservation. Finally, a considerable amount of research is performed in the field of xenotransplantation.9

Types of stroke in kidney disease
Autosomal dominant polycystic kidney disease (ADPKD) is a life-threatening single-gene disease with significant morbidity and mortality. The disorder is characterized by the formation of cysts in multiple systems and an increased risk of intracranial aneurysms. 50% of affected individuals developing end-stage renal disease [22, 23].

Lee et al. set out to perform a retrospective cohort study based on the Taiwanese population to document the incidence rates of different types of stroke among close to 8000 patients with ADPKD. The incidence rates of stroke were increased in general in the patient group with ischemic stroke as the most frequent stroke type [24].
Refined techniques to observe changes in white matter

The rare autosomal recessive disorder cerebrotendinous xanthomatosi
on (CTX) is characterized by lack of the mitochondrial enzyme sterol 27-hydroxylase, thus preventing the conversion from cholesterol to bile acid. The consequent accumulation of cholesterol deposits and related compounds entails damage to the brain, spinal cord, tendons, eyes, and arteries. A medical therapy with chenodeoxycholic acid (CDCA) is considered standard for CTX [25]. Since the progress of CTX is slow, the use of conventional magnetic resonance imaging (MRI) is not sufficient to monitor treatment response over short period of time. Hence imaging techniques providing more detailed insights are employed [26]. Such tools include diffusion tensor imaging (DTI) and fiber tractography (FT). DTI is an MRI technique that allows to estimate the organization of white matter (WM) of the brain, and FT delivers a 3D reconstruction, allowing assessment of neural tracts.11

Lee et al. used diffusion kurtosis imaging, an extension of conventional DTI, and FT to evaluate WM changes in two CTX patients. The two siblings had previously received CDCA treatment for 10 years but stopped it three years ago. The imaging study concluded that DKI and cerebral tractography facilitate the identification of changes in cerebral WM in CTX patients shortly after stopping CDCA treatment. The imaging results correlate with the subtle cognitive decline identified through neuropsychiatric studies [26].

If it cannot be cut, it should be burned

The application of thermal therapy to treat mass lesions nowadays known as cancer has been used for around 4000 years in medical practice but also by lay people. The Greek physician Hippocrates, who lived around 400 BC, advised that if a tumor cannot be cut, it should be burned, and if it cannot be burned, then it is incurable. There are multiple forms of hyperthermic therapy including local, regional, and whole-body approaches [27].

In ovarian cancer, the outcomes of hyperthermic intraperitoneal chemotherapy (HIPEC) are evaluated in a mixed way. Some consider the current data as not convincing [28], whereas other results showed HIPEC in combination with cytoreductive surgery (CRS) is effective against ovarian cancer [29]. Chen et al. performed a retrospective review of outcome and morbidity in secondary CRS and HIPEC in recurrent ovarian cancer. Despite the limited sample size, the study provides an insight into the option of salvage therapies for patients. Adding HIPEC to secondary CRS might not only prolong progression free survival, but furthermore decrease intraperitoneal recurrence [30].

The Sun King on his toes

Ballet evolved as a specific dance style from the 14th century Renaissance Italy. The Italian banker family the Medici were a driving force in advancing art and humanism across Europe. Thanks to them, ballet in its form back then became popular as a court dance in France. Louis XIV performed his 12 h “Ballet de la Nuit” (ballet of the night) in 1653, where he appeared at the end of the performance as the daylight, saving his country. This event made him famous as Roi de Soleil (Sun King), and was major in enhancing the popularity and rapid evolution of ballet [31]. A common belief over the centuries was that the perfect ballet dancer foot requires very high arches, as those were considered aesthetically most pleasing, and training was accordingly geared towards that goal. However, considering the amount of stress and load a dancer’s feet needs to bear especially during the pointe technique, it is more favorable to have an intermediate arch. As a result the foot mechanic will provide the ballet dancer with stability and support for being able to stand on their toes, which they do on average 48 h per working week [32].

Chang et al. performed a longitudinal prospective study to investigate the development of foot arches in children. In boys, a critical factor for foot arch development was the ability to balance on one leg, whereas in girls it was less increase in body height over time [33].

Precision radiation therapy

Stereotactic body radiation therapy (SBRT) is an image-guided procedure enabling the delivery of a single, high tumoricidal dose while sparing the surrounding, normal tissues to a maximum [34]. Treatment is usually concluded within the course of only 1–2 weeks and a total of 3–5 sessions. The accurate mapping in SBRT permits a tailored approach according to the patient’s anatomy, and therefore a precise radiation treatment. A comparable level of precision is usually only achieved for tumors in the CNS, as tumors and organs outside of the CNS potentially moving with breathing and other factors.12

The combination of SBRT plus cetuximab has been revealed as promising in the case of unresectable recurrent head and neck squamous cell carcinoma (rHNSCC), although rare reports exist for patients in Asian countries. Huang et al. hence performed an according study with 74 patients in Taiwan. Taiwan shows one of the highest incidences of HNSCC in the world which the authors suggest might be due to the habit of smoking and chewing of betel quid in the Taiwanese population. The treatment approach proved to be a feasible salvage strategy for patients with previously irradiated but unresectable rHNSCC [35].

Letter

Renal impairment and serum cancer antigen-125

Bello et al. answer to an article by Chen and colleagues [30] since the relation found between renal impairment and serum

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10 https://rarediseases.org/rare-diseases/cerebrotendinous-xanthomatosi/, last access 09/22/2022.
11 https://radiopaedia.org/articles/diffusion-tensor-imaging-and-fibre-tractography, last access 09/22/2022.
cancer antigen-125 (CA-125) in recurrent ovarian cancer patients caught their attention. The team suggests that CA-125 should be included as a biomarker before hyperthermic intraperitoneal chemotherapy (HIPEC) for determining potential nephrotoxicity of some drugs administered [36].

Chen et al. recognize the hypothesis and emphasize that kidney function has always been of importance for patients receiving HIPEC with cisplatin-containing regimen. They reference other risk factors of acute renal injury and suggest using RIFLE classifications to assess post-operative renal function. Also, they perceive a need for further assessment of the relationship between CA-125 and acute kidney injury [37].

Disclaimer
None.

Conflicts of interest
The author declares no conflicts of interest.

Acknowledgments
None.

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