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EDITORIAL

Issues and Impact of COVID-19 on Surgical Services in Northern Borneo, Sabah

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Globally, everyone has gone through an unusual and remarkable period during the COVID-19 pandemic. The pandemic has affected various sectors in the country and implicated society. Important services including the health care system, particularly in surgery, have raised challenges and issues that need to be sorted out. This action is prudent to justify the balance in between care on preventing the spread of COVID-19 infection and at the same time providing surgical services. In this article are the perspectives on how we elicit the issues and the solutions in providing surgical services during the COVID-19 pandemic in our state, Sabah.

The COVID-19 pandemic has released turmoil all over the world. Respective governments and other organisations are actively responding to curb the spread of the damaging virus. As of 26th June 2021, there were more than 180 million confirmed COVID-19 cases reported worldwide with an average number of 370,000 cases reported per day, in addition to global deaths of almost 4 million (World Health Organization [WHO], 2021). Industrial sectors such as tourism, food production, finance, trading, and properties as well as healthcare services have been greatly affected. Many hospitals and health institutions especially the tertiary centres have been involved in this calamity. Among all crucial services in the hospital, surgery and its subspecialties are among the worst units being affected. In general, they can be broadly

categorized into (1) surgical personnel, (2) surgical practice and services, and (3) surgical procedures on patients.

Surgical Personnel

Surgeons and surgical staff are among the healthcare personnel that are heavily involved from staff nurses in the clinic, gastrointestinal assistants in the endoscopy room, assistant nurses in the operation theatre, medical officers, postgraduate surgical trainees and surgeons. All are involved in providing equivalent responsibility in managing surgical patients.

Post-graduate training is a core process in preparing the nation with a continuous supply of new-breed surgeons and the need for personnel within the fraternity. However, due to this pandemic, the whole training schemes are needed to be channelled for a greater need, fighting COVID-19. Speciality rotation, exposure to elective procedures, end of posting assessment, and speciality exit examination are affected and postponed to a later date during this MCO. The structures of exit examination in surgery speciality programs are mostly face-to-face in which involve more in the psychomotor domain. It is yet to be determined whether the assessment system requires any revamp to suit the new norm post-pandemic event. Hence, it delays the production of a new breed of surgeons in the country.

Human resources are restructured to fill up the need to ensure the COVID-19 core front liners on screening and managing COVID-19 services are at optimum. Medical officers are being relocated to help the frontliners in the screening team as the manpower available is inadequate to battle the pandemic. They have been deployed to other services and units to provide much-needed care, again for the greater benefit. The training of housemen in a tertiary centre will be slightly affected. They are the people who have freshly graduated from medical school, require training in the medical field to the fullest. Being involved in the COVID-19 pandemic, their training will slightly deviate from the norms. Usual round, common elective cases, and clinic and surgery sessions, all are catered following the standard operating procedure of COVID-19.

Surgical Practice and Services

There are several modifications in surgical practices and services that need to be made during the COVID-19 pandemic. The first action that was taken by the nation's health department and the involved tertiary hospitals is by preparing all the possibilities for COVID-19 to spread out of control including higher education institutions (Mukhsam et al., 2020). This organization and preventive approaches are mandatory in the phase of MCO. This is to ensure the capability and competency as well as preservation of financial and human resources. In Sabah, one of the tertiary hospitals was converted to a COVID-19 hospital. All surgery-related services including the vital surgeries and devices for surgery were transferred to another hospital. Even though the process of transferring all the equipment is following the standard of procedure, the risk of malfunction and loss throughout the transfer process may still happen.

Due to geographical challenges and lack of surgeons, we have to adopt the initiation of visiting surgery services in the district areas. However, this service has to be put on halt due to this pandemic. This is to ensure that the enforcement of human resources in surgery is centred on tackling COVID-19 matters at tertiary centres. Previously, the monthly visits to the involved district can help to reduce the high burden of cases backlog at the district level. Any low-risk procedures can be performed during these visits, hence reducing the cases in tertiary centres.

To avoid overcrowding in the waiting area, the number of cases for clinic appointments is being cut down. Patients

are selectively chosen to be seen in the clinic. Chairs in the waiting areas are spaced out to avoid physical contact and social interaction. Waiting time for speciality consultations is now being pushed longer than before. Certain hospitals refuse to accept patients with the slightest of respiratory symptoms in fear of the COVID-19.

Surgical Procedures on Patients

Any elective cases such as benign cases and certain cancer patients need to be postponed until the infection has been considered cleared by the authority. Emergency and complicated cancer patients with bleeding, obstructed, or perforated tumours are deemed to be surgically intervened as early as possible. A decision has been made at many hospitals and health institutions to postpone elective operations in keeping with recommendations by the American College of Surgeons (Begley et al., 2020). Upon managing these patients, participation and involvement of all surgery-related personnel must be minimal. Duration of the surgery needs to be fastened, the number of assistants is limited, and complicated or big cases are to be performed by senior medical officers or surgeons.

Better to add different hospitals in peninsula Malaysia and Sabah's surgical management procedure during COVID-19 both inpatient and outpatient departments and compare with other countries management during the same period.

Operation theatre (OT) is the most important area in surgery as it is the place where most elective and emergency cases reside. Activities of going in and out of the OT are prohibited. Personnel present in the OT during surgery must not leave the room. Any sudden essential retrieval of necessary equipment should be done by staff outside the OT. After finishing the cases, logistics should decontaminate the OT before the next procedure takes place, to reduce possible air contamination. After the case, all areas at risk of contamination must be cleaned and disinfected. Efforts should be made to minimize the contamination risk associated with specimens sent to the pathology department.

Both patients and treating doctors are at high risk to be exposed to the COVID-19 virus through the aerosol-generating procedure (AGP) such as laparoscopic surgery and endoscopic procedures. The choices between open and laparoscopy are debatable among the surgical fraternity. Any cases that can be treated using an open technique with minimal risk are advised to do so. Laparoscopic surgery is best to be avoided to reduce the risk of viral transmission from AGP. The possibility of viral contamination can occur via the possible release of a virus in the form of an aerosol with CO2 (Pryor, 2020). During laparoscopy, a jet of air is to be blown through the trocars giving a chimney effect. Consequently, the operating theatre will be concentrated with aerosol materials, especially viruses hence exposing the operating staff to viral contamination (Mowbray et al., 2020). Few recommendations have been suggested for laparoscopy among unknown COVID-19 status patients (Joseph et al., 2020). Similarly, elective endoscopy procedures especially for diagnostic and screening purposes are withheld to give way to only emergency cases.

In conclusion, the COVID-19 pandemic has caused a huge implication to various areas and sectors in the services of surgery. Most importantly, protecting the health care personnel and patients are the utmost crucial aspect during this pandemic. The issues and challenges can highlight the authority and relevant parties to be prepared and react wisely to balance between further disease spread and providing surgical services to the community.

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REVIEW ARTICLE

Knowledge Synthesis in Health, Wellness and Social Care Research: The Fundamentals of Conducting Comprehensive Reviews

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ABSTRACT

Knowledge synthesis is often a term that is widely used to define the process of summarizing and integrating research findings into the existing field of research of a specific topic. While knowledge syntheses can take many forms, it is commonly produced as a review of previously published literature in a specific field. With the recent tremendous increase in scientific, especially health, publications, conducting literature reviews has become an absolute necessity for investigators to scope out the body of research work that has already been done. Literature reviews provide a unique function of providing a clear and articulate understanding of the extent of previous work that has been done such that resources are not wasted in redundant duplication. Moreover, literature reviews can serve multiple purposes such as providing context to current crises, efficiently summarizing previously published work, identifying gaps in the literature of a specific topic, and aiding the overall advancement of knowledge in the research field of interest. In this manuscript, we provide detailed general steps for conducting a review based on standard and common methodological frameworks used to inform and conduct knowledge syntheses.

INTRODUCTION

Knowledge synthesis is often a term that is widely used to define the process of summarizing and integrating research findings into the existing field of research of a specific topic (Grimshaw, 2010). They are generally done to contextualize research findings within the global evidence of research done, thus

providing investigators with what has been done and what still needs to be investigated. These knowledge syntheses can be conducted by gathering information on a specific topic from different sources of information (original research, previously published research, grey literature, academic publications, etc.) (Kastner et al., 2012).

While knowledge syntheses can take many forms, it is commonly produced as a review of previously published literature in a specific field (Grimshaw, 2010). Synthesis of previously published literature can be presented in a wide range of ways such as systematic reviews, scoping reviews, rapid reviews, meta-analyses, meta-syntheses, etc. Such reviews allow the researchers to be up to date with the current research landscape and to identify the gaps in the current literature so new research can be initiated to address these gaps.

With the recent tremendous increase in scientific, especially health, publications, conducting literature reviews has become an absolute necessity for investigators to scope out the body of research work that has already been done. Literature reviews provide a unique function of providing a clear and articulate understanding of the extent of previous work that has been done such that resources are not wasted in redundant duplication (Samnani et al., 2017). Moreover, literature reviews can serve multiple purposes such as providing context to current crises, efficiently summarizing previously published work, identifying gaps in the literature of a specific topic, and aiding the overall advancement of knowledge in the research field of interest.

General Steps to Conducting a Review

In this manuscript, we will provide detailed general steps to conducting a review based on standard and common methodological frameworks used to inform and conduct knowledge syntheses (Ahmed et al., 2016; Samnani et al., 2017). These steps provide general guidance for anyone conducting a literature review. Figure 1 outlines the steps of conducting a review.

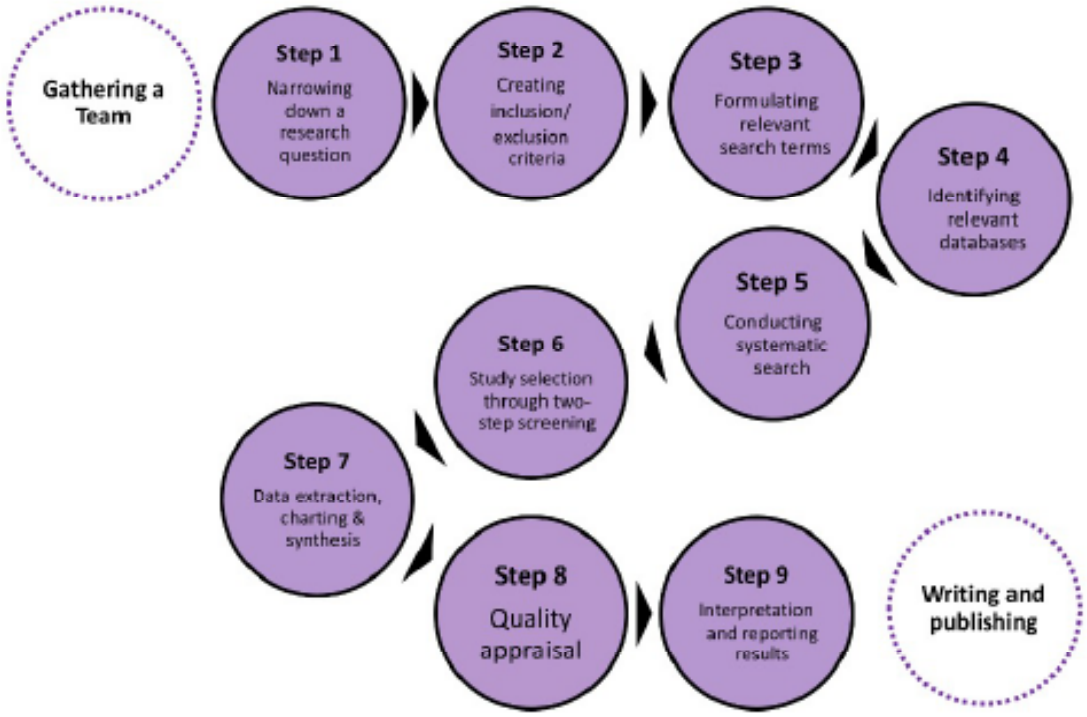

Figure 1 General steps of conducting a review

Step 1: Focusing on a research question

To conduct a review, investigators need to develop a research question first that is reflective of the objectives, scope, and specific inquiries of the review. The research question and objectives of the review will ultimately shape the inclusion/exclusion criteria, therefore, dictate the capture of information done through knowledge synthesis. There are a few established frameworks that can be used to inform and formulate the research question. The PICOS framework is one of such frameworks that is often used by researchers to recognize the scope of the research question (Schardt et al., 2007). PICOS stands for Population, Interventions, Comparison, Outcome, and Study design. The PICOS are generated based on the research question.

Step 2: Creating exclusion/ inclusion criteria

Following the formulation of the research question, investigators may develop inclusion/ exclusion criteria, which will determine how comprehensive or specific the knowledge synthesis will be (Ahmed et al., 2016). A well-defined inclusion/exclusion criterion will inform the researchers and readers about the breadth and depth (scope) of the review article (Lockwood et al., 2019). The inclusion/exclusion criteria act as a guide for the investigators as it informs them which information to accept into the review and which information to reject. Firm reasoning and justification can be provided behind each inclusion/exclusion criterion to make the study approach clearer for the readers (Tricco et al., 2018). Further, the timeline of the research and the languages included in the review are stated at this stage (Ahmed et al., 2016).

Step 3: Formulating relevant search terms

To find the studies that have been done before, researchers need to identify a set of relevant keywords to be used in a systematic search. Given its essential nature, formulating relevant keywords is a crucial step as it yields the articles relevant to the context of the synthesis (Ahmed et al., 2016). To formulate optimized keywords, investigators initially perform a limited search on the topic of interest. This initial search serves the function of informing the investigators about relevant keywords as they can scan the title and abstract of relevant literature for them (University of Tasmania, 2021). The limited search also helps shape the scope of the review further as the researchers can recognize the keywords that are specific to the topic and will yield the most optimized results (yielding of most relevant articles from a systematic search of databases) (Ahmed et al., 2016). Furthermore, this search allows the investigators to have a look at relevant search databases as well, therefore allowing the investigators to recalibrate and optimize their entire search strategy for desired results (Chowdhury & Turin, 2019).

It should be noted that search terms are often dichotomously categorized into Medical Subject Heading (MeSH) and keywords. Medical Subject Headings or MeSH terms are keywords that have been created and used by the National Library of Medicine to categorize and archive information/literature relating to medicine and health (U.S. National Library of Medicine, 2012). As these terms have been used by other researchers who have published works, they are quite useful in yielding relevant articles when included in the search strategy for the systematic search. Keywords are more straightforward in their definition; in that, they are phrases or words that can be utilized for searching a database. To come up with the most relevant keywords for the search, investigators may want to break down the main research question, each section of the PICOS, and the purpose of the review into fragmented parts. After this division, the investigators can formulate relevant keywords for each specific component, which can then be combined for the systematic search to yield the most relevant literature.

Step 4: Identifying relevant search databases

(a) Academic Data Sources

Once the keywords have been created and finalized by the investigators, relevant search databases need to be identified for a systematic search (Ahmed et al., 2016). Most electronic search databases are specific to the topic of interest, and therefore the researchers try to identify and evaluate how relevant the database is to their topic of interest (Lefebvre C et al., 2019). As mentioned in the previous step, a limited search can inform the investigators about relevant search databases that will yield the most optimized results for the knowledge synthesis. In parallel with the keywords, relevant databases are also informed by the primary research question. For example, for a very clinical question, we will need to make sure that we include the databases which were predominantly a source for clinical studies (Bramer et al., 2018). On the other hand, a review study focusing on the social determinants of health issues needs to include all the broader health and wellness research databases. To find the most relevant articles, it is recommended that the investigators search as many relevant databases as possible as it would exhaustively address the primary research question, ensuring a lower chance of missed relevant articles (Ahmed et al., 2016). It should be noted that this process will often produce large quantities of duplicate articles. However, these duplicates can be easily removed by appropriate referencing software. Table 1 presents different academic literature databases which are conventionally used for conducting reviews for health research.

Table 1 A sample list of databases to be searched to identify literature for this synthesis

Published articles	Grey literature
Health sciences: • MEDLINE (Ovid) • EMBASE • PsycINFO • HealthSTAR • PubMed • PubMed Central • CINAHL • MEDLINE (Ebsco) • TRIP • EBM Reviews *Social sciences:* • Social Science Data Archive • SocIndex with FullText • Sociological Abstracts • Social Work Abstracts • Psychology & Behavioral Sciences Collection *Political science:* • International Political Science Abstracts • PAIS Index *Multidisciplinary:* • Web of Science • Urban Studies Abstracts • Scopus • Canadian Research Index • LegalTrac • Business Source Complete	*Academic-focused search engines:* • Google Scholar *Repositories/theses:* • ProQuest (theses and dissertations) • OAISter (WorldCat) *Health sciences:* • Health Sciences Online (HSO) • Turning Research into Practice (TRIP) • Canadian Institutes of Health Research (CIHR) • Canadian Institute for Health Information (CIHI) • Public Health Agency of Canada (PHAC) • Health Canada • National Institutes of Health (NIH) • World Health Organization (WHO) • National Health Services (NHS) • Alberta Health Services (AHS) Insite *Social sciences:* • Federation of Data Organizations for Social Science (IFDO) • Consortium of Social Science Associations (COSSA) • Organization for Social Science Research in Eastern and Southern Africa (OSSREA) • International Organization of Social Sciences and Behavioral Research (IOSSBR) • International Federation of Social Science Organizations (IFSSO) • Government of Canada: Immigration and Citizenship

(b) Grey Literature Data Sources

In congruence with academic databases, the investigators also search for the grey literature sources to understand the complete scope of their extensive systematic search. Due to the rapid nature of information production in today's world, grey literature has become an essential part of knowledge synthesis to understand the global evidence regarding the topic of interest. Grey literature is defined as rapid and non-conventional sources of information that include a variety of different documents and sources of information such as government documents, websites, blogs, etc. (Schöpfel & Farace, 2010). Google and Google scholar are search engines that are often used for searching grey literature, given the expansive collection of information that exists within these search engines (Vaska et al., 2019). Just like academic databases, grey literature databases are also specific to the topic and should be identified accordingly. Table 1 presents several grey literature databases or repositories that are commonly used for conducting reviews in health and social science-related research topics. Figure 2 shows a larger number of potential grey literature sources.

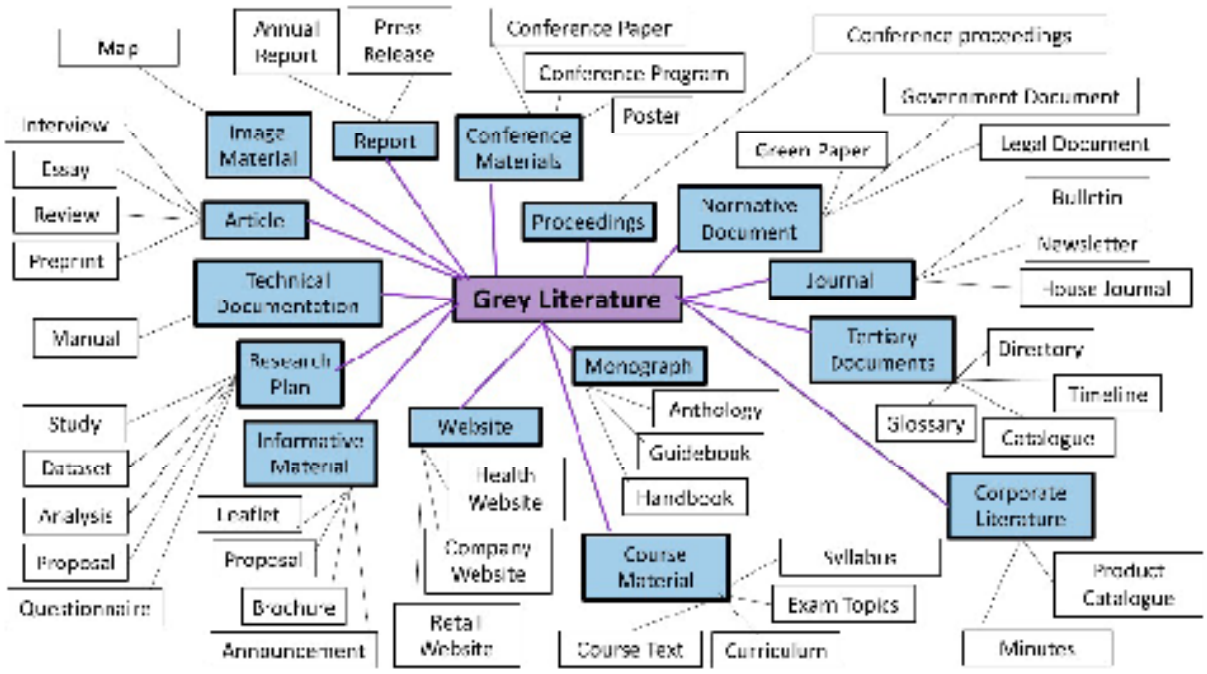

Figure 2 Grey literature typology

Step 5: Conducting a systematic search

After finalizing the relevant keywords and databases, we conduct a systematic search (Ahmed et al., 2016). To do so, a search strategy needs to be created by the investigators. Much like the previous two steps, the search strategy needs to be reflective of the primary research question. This is done by creating a comprehensive and specific search strategy that reflects the objectives of the review and is robust enough to capture the most relevant articles to the research question (Ahmed et al., 2016). Search strategies are specific to databases and may need to be adjusted (different keywords and headings) accordingly to capture all relevant articles from each database (Bramer et al., 2018). Creating a search strategy is often done by the use of Boolean operators "OR" and "AND" to combine the keywords and MeSH terms generated in the previous steps. First, the search terms within each

component of the research question (informed by the PICOS framework) are combined using the "OR" function to provide a wide scope of capture (Methley et al., 2014). The results from this stage are then further combined using the "AND" function to execute an exhaustive systematic search that is reflective of the research question in its entirety.

As the grey literature realm is quite rapid and expansive in its manner of knowledge production, grey literature database searching is focused primarily on using keywords to perform the systematic search (Vaska et al., 2019). Much like academic databases, keywords from within each component of the research question are combined by using Boolean operators "OR" and then these results are combined with the Boolean operator "AND". These keywords are then used to search Google Scholar and Google, as these act as the fundamental search databases for capturing information from grey literature. Due to the algorithm that dictates the relevancy of information, this search is often limited to the first 100 results or 10 pages (Canadian Agency for Drugs and Technologies in Health [CADTH], 2018).

Step 6: Study selection through a two-step screening

To conduct reviews, the investigators need to be able to identify relevant articles from the vast body of information that will not be relevant to the purpose of the knowledge synthesis. To screen out irrelevant information, investigators perform a two-step screening as it allows them to proceed with only the most relevant information for the review. This process has two phases: title and abstract screening and full-text screening.

(a) Title-Abstract Screening

During the title and abstract screening phase, generally, two independent investigators commence the screening at the same time (Tricco et al., 2018). They screen the abstract and title of every article that has been yielded through the systematic search. As the investigators independently comb through the title and abstract of each article, they scrutinize if the information presented meets the established inclusion criteria. If an article does meet all the requirements, it can then be graduated to the second phase (full-text screening). If the information presented in the title and abstract of the yielded literature is deemed to be inconclusive, thus creating doubt, then it can be modified to be included for the full-text screening phase (Lockwood et al., 2019).

(B) Full-Text Screening

Once all the titles and abstracts have been thoroughly screened, the investigators move on to the full-text screening phase. This stage consists of the investigators reading the entire text of each article that was included in the first stage. A full read of the articles will inform the investigators undoubtedly about their decision to either include or exclude the article from the review. If disagreements arise between the decisions for inclusion made by the individual investigators, then both investigators collaborate and use the inclusion criteria to decide on the article in question. At the full-text screening phase, the final decision to either accept or reject articles for the review is made. Investigators can also employ other methods such as Pearl Growing, Snowballing, or Citation Mining (Icahn School of Medicine at Mount Sinai, 2020), where the references of selected articles are thoroughly scanned to find other potentially missed papers. As this process is thorough, software such as Covidence, MS Excel, EndNote, and RefWorks are often utilized to facilitate the process.

Step 7: Data extraction, charting, and synthesis

After finalizing the study selection stage, the information presented within these studies is extracted and organized appropriately. About presenting the information, reviews provide a

high degree of freedom for the investigators to do so as they see fit for the knowledge synthesis (Samnani et al., 2017). It is important to keep in mind that information should be presented in a way that is coherent, logical, and easy to follow for the readers (Tricco et al., 2018). Information can be presented in the form of tables, charts, figures, or diagrams. The information that is extracted and presented needs to be aligned with and reflective of the primary purpose of the knowledge synthesis (Ahmed et al., 2016). As mentioned earlier, there is a multitude of different ways to present information that has been extracted from selected articles. However, in general, the first table of the review describes the studies that were included in the knowledge synthesis. Information such as year of publication, demographic information, author, place of research, research methods, etc., can be listed here. The following tables and figures are completely at the discretion of the investigators and their choices of presenting the findings in a way that reflects the overarching objective of the review.

Step 8: Study quality appraisal

An important step of the knowledge synthesis is the appraisal of the quality of the sources of evidence. However, it is not mandatory for all reviews but strongly recommended for certain types of reviews that entail a deeper level of syntheses such as a systematic review and meta-analysis. To evaluate the sources that are eligible for the final level of the synthesis, a predetermined set of criteria is used. Generally, the criteria include various characteristics of the articles such as objective, methods, interventions, etc. Differently structured checklists are available that can be used for a quality appraisal (Shepherd et al., 2013). However, the appropriate quality appraisal tools/checklists need to be employed according to the type of the study (e.g., quantitative or qualitative) (Chowdhury & Turin, 2019).

Step 9: Interpretation and reporting results

Investigators now need to summarize the extracted information from the research articles and present it coherently and logically such that it is aligned with the research question being investigated in the knowledge synthesis (Samnani et al., 2017). By this stage of the process, the information has been extracted and charted and therefore it can be organized and summarized at the discretion of the investigators (Lockwood et al., 2019). Often, themes can be found within the extracted information, leading to the thematic categorization of this information being presented in the review (McKenzie & Brennan, n.d.). This categorization should reflect the aims of the research question and so it is fully dependent on the results that were yielded from the articles included in the review. At this stage, investigators should also state the gaps that exist in the literature as this gives readers an understanding of the research landscape and inform them about future research that needs to be done.

Different Types of Reviews

Review Typology

There are different types of reviews. The choice of which type of review to conduct is often governed by the purpose of the study and the breadth and depth of information synthesis. The specific characteristics associated with the different types of reviews are provided in Table 2. Table 3 describes the major features of different types of reviews based on the Search, Appraisal, Synthesis, and Analysis (SALSA) analytical framework (Grant & Booth, 2009).

Table 2 Characteristics of common types of reviews

Type of Review	Key Attributes	Strengths	Deficiencies
Literature Review / Narrative Review / Overview Review	• Evaluate the current literature on a particular topic • Need specific inclusion criteria for selecting studies	• Consolidate previously known knowledge • Comparatively quick to perform	• Does not emphasize analyzing collected data • Does not require a formal systematic search, thus generating the possibility of bias by omitting or limiting a search
Scoping Review	• Evaluate the potential scope of literature available on a particular topic • Identify the extent of resources available, including ongoing research	• Identify the need for full systematic review • Identify gaps in the literature for future research • Update researchers, policymakers about the extent of work already done	• Lack of quality assessment risks the inclusion of studies based on their existence rather than their intrinsic quality
Integrative Review	• Encompasses the broadest ranging research methodologies to capture information from both non-experimental and experimental data • Utilizes both empirical and theoretical information	• Inclusion of a diverse set of methodologies • This can lead to theory development • Direct application to policy and practice	• The incorporation of diverse methodologies can lead to inaccuracy and bias in the review • Combining empirical and theoretical data can potentially lead to complicacy
Critical Review	• Critically evaluate effectiveness and quality of cited resources • A reader can make a judgement about the topic of interest	• Extract information critically • Quick and elaborated overview • Often involves competing schools of thought	• Lack of systematic search • No formal quality assessment • Review is subjective and depends on the authors' expertise
Systematic Review	• Includes systematic approach for searching literature following a standard scientific protocol • Prime importance in evidence-based research • Identify reliable and quality data	• Gather and assess the quality of all the scientific knowledge on a particular topic • Reduces bias because of its systematic nature	• Dependent on the quality of the selected studies.
Meta-Analysis	• Develop precise statistical outcomes of multiple quantitative studies • A reader can get an idea about population characteristics and results • Requires all included studies to have sufficiently similar measures	• Assimilation of conclusive and statistically significant studies create a solid evidence base for practice • Overcomes the issue of the small sample size of individual studies • Increases precision of estimating effects	• The inappropriateness of combining studies not similar enough weakens the finding

Mapping Review	• Map out and classify existing literature on a topic • Differs from scoping review, as the outcome is not known beforehand, and the findings of these reviews will open doors to further analysis	• Enables contextualization of detailed literature • Important for policymakers or decision-makers to deal with practice-relevant review questions • Also determines population characteristics	• Time constrained and lacks a systematic approach • May oversimplify or mask the significant points • No quality assessment of cited resources
Qualitative Systematic Review	• Integrate and compare the outcome of qualitative studies • Interpret the findings in a broader aspect on a particular subject	• Compliments quantitative research evidence • Being generalized increases its worth compared to local surveys	• No specific methodology
Meta-Synthesis	• Describe, interpret and transform data from multiple qualitative studies • Aims to determine the explanation for particular phenomena as opposed to a meta-analysis that focuses on quantitative outcomes	• Involves a rigorous and systematic approach • Identifies common core elements and themes • Non-statistical technique	• Including irrelevant studies will decrease the effectiveness of the review • Studies without a clear description of each step of review will not be quickly adopted for EBM
Realist Review	• Deals with finding outcomes related to complex interventions • Aims to seek explanatory focus	• Includes relevant studies because of its systematic methodology • Explains the outcomes of findings rather than judging results	• Uses argumentation analysis to deal with identifying context and mechanism of the study • Complicated and time-consuming for reviewers
Review of reviews/ Umbrella Reviews	• Extracting outcomes from multiple reviews	• Easier for a reviewer to go through a single review • Helpful for decision-makers	• Requires pre-existence of the narrowest component of reviews
Mixed Methods Review / Mixed Studies Review	• Combines results from both quantitative and qualitative sources within a review	• Can address multiple questions in one review	• Requires great methodological skills
Rapid Review	• Synthesize knowledge in a quick turnaround time	• Allows for knowledge synthesis in a short period • Pragmatic uses for what has been done in policy or practice and also new and emerging research	• Search is not as comprehensive (limited amount of information sources)

Adopted and reproduced from Ahmed et al. (2016). Conducting a literature review in health research: basics of the approach, typology, and methodology. JNHFB 2016;5(2):44-51.

Table 3 Common types of reviews are explained using the Search, Appraisal, Synthesis, and Analysis (SALSA) framework

Type of review	Methods used by SALSA			
	Search	**Appraisal**	**Synthesis**	**Analysis**
Literature Review / Narrative Review / Overview Review	• May or may not include comprehensive searching	• May or may not include quality assessment	• Typically, narrative	• Analysis may be chronological, conceptual, thematic, etc.
Scoping Review	• Completeness of searching determined by time/scope constraints. May include research in progress	• No formal quality assessment	• Typically, tabular with some narrative commentary	• Characterizes quantity and quality of literature, perhaps by study design and other key features. Attempts to specify a viable review
Integrative Review	• Using multiple search strategies to conduct the most exhaustive search to capture maximum literature	• Quality assessment	• Tabular	• Identifying themes and patterns through critical analysis and creativity
Critical Review	• Seeks to identify most significant items in the field	• No formal quality assessment. Attempts to evaluate according to contribution	• Typically, narrative, perhaps conceptual or chronological	• Significant component: seeks to identify conceptual contribution to embody existing or derive new theory
Systematic Review	• Aims for exhaustive, comprehensive searching	• Quality assessment may determine inclusion/exclusion	• Typically, narrative with tabular accompaniment	• What is known; recommendations for practice. What remains unknown; uncertainty around findings, recommendations for future research
Meta-Analysis	• Aims for exhaustive, comprehensive searching. May use funnel plot to assess completeness	• Quality assessment may determine inclusion/ exclusion and/or sensitivity analyses	• Graphical and tabular with narrative commentary	• Numerical analysis of measures of effect assuming absence of heterogeneity
Mapping Review	• Completeness of searching determined by time/scope constraints	• No formal quality assessment	• May be graphical and tabular	• Characterizes quantity and quality of literature, perhaps by study design and other keys features. May identify a need for primary or secondary research
Qualitative Systematic Review	• May employ selective or purposive sampling	• Quality assessment typically used to mediate messages not for inclusion / exclusion	• Qualitative, narrative synthesis	• Thematic analysis, may include conceptual models

Meta-synthesis	• Aims for rigorous, systematic search of relevant studies	• Quality assessment may determine inclusion/exclusion and/or relevance	• May involve narrative commentary with tabular and graphical representation	• Interpret and transform findings from multiple qualitative studies to reflect the explanation of the phenomena
Realist Review	• Formal Systematic search	• Assessment of relevance and rigour	• Typically, tabular with some narrative commentary	• Identify the attributes of 'what works, how, for whom, in what circumstances and to what extent for any intervention
Review of Reviews / Umbrella Reviews	• Identification of component reviews, but not primary studies	• Quality assessment of studies within component reviews	• Graphical and tabular with some narrative commentary	• What is the known recommendation for practice • What remains unknown; recommendation for future research
Mixed Methods Review / Mixed Studies Review	• Distinct searches for qualitative and quantitative literature	• Generic assessment tools/individual assessment processes	• Graphical, narrative, and tabular	• What correlations exist between characteristics • Identify gaps in the information
Rapid Review	• Limited systematic search as time allows	• Uses systematic review methods to critically assess literature as time allows	• Narrative and tabular	• What is known about a specific topic • Looks primarily at the quantity of research and overall direction of research

Adopted and reproduced from The details of The Search, Appraisal, Synthesis, and Analysis (SALSA) framework presented with permission from John Wiley and Sons from the following reference: Grant MJ, Booth A. A typology of reviews: an analysis of 14 review types and associated methodologies. Health Information & Libraries Journal. 2009;26(2):91-108.

Depth of Synthesis

There is one point that we would like to bring forward for the readers. The depth or intensity of synthesis, desired by the researchers, is one aspect regarding the types of reviews (Whittemore et al., 2014). In some instances, the researchers might not need to go deep into a topic, rather they may simply want to understand the current research landscape of the topic (Samnani et al., 2017). In this case, choosing a scoping review will be sufficient for their purpose (Lockwood et al., 2019). On the other hand, researchers might want to understand in-depth how exposure is related to an outcome. In this case, the researchers will need to conduct a meta-analysis level review, which requires a more rigorous methodology (Chowdhury & Turin, 2019). Figure 3 provides a conceptual framework regarding the depth of analysis and different types of reviews.

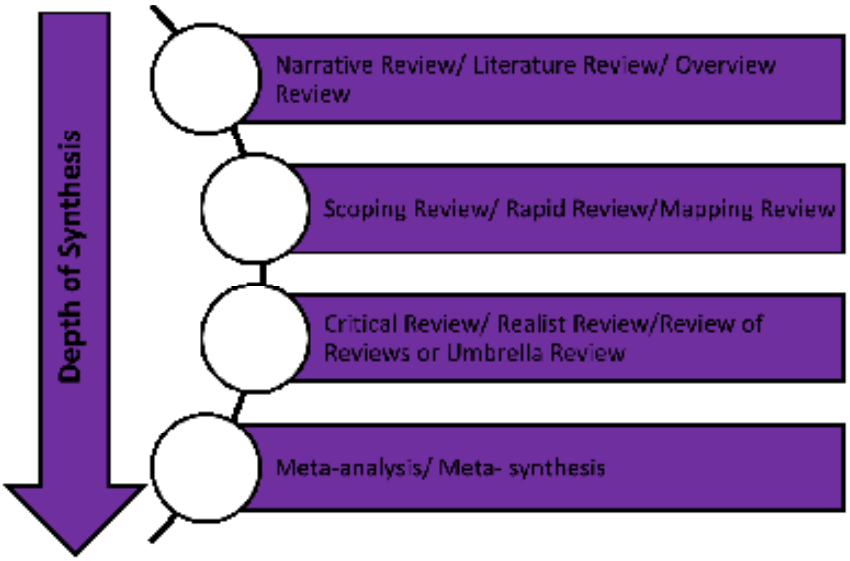

Figure 3 Depth of synthesis and review types

Precision and Confidence of Synthesized Results

It is quite natural that the more in-depth the analysis is, the more the precision of the results will be. So, in one sense, the type of review is also associated with the levels of the rigour of the results synthesized (Samnani et al., 2017). Also, we need to recognize that, in lots of instances we do not need to aspire for precision. For example, a scoping review to summarize health care access barriers faced by the racialized communities does not require in-depth analysis toward precision. On the other hand, a meta-analysis to summarise the effect of early childhood traumatic events on mental health outcomes during adulthood will need rigorous analysis. Also, we need to acknowledge that the more rigour we would like to achieve, the more time, resources, skill sets will come into play while conducting reviews (Whittemore et al., 2014). For example, a scoping review can be done in a relatively shorter time than a meta-analysis. Also, a scoping review does not warrant as many high analytical skill sets as a meta-analysis. Figure 4 provides a conceptual framework regarding the precision-confidence of results, time-resource-skill needs, and review types.

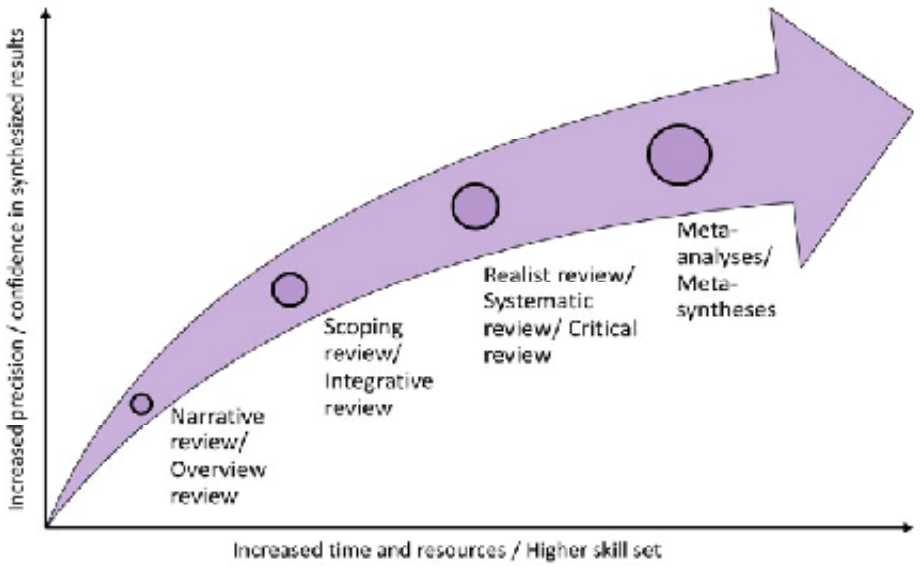

Figure 4 Precision and confidence of results, time-resource-skill needs, and review types

Writing a Review Manuscript

In an academic environment, the conventional final step in conducting a review is to prepare and publish a manuscript. The manuscript acts as a final product of the knowledge synthesis as it can be submitted to journals for publication and therefore contribute to the total body of research that has been done on the specific topic. A review manuscript generally consists of several components and Figure 5 outlines a skeleton of different components of a review manuscript.

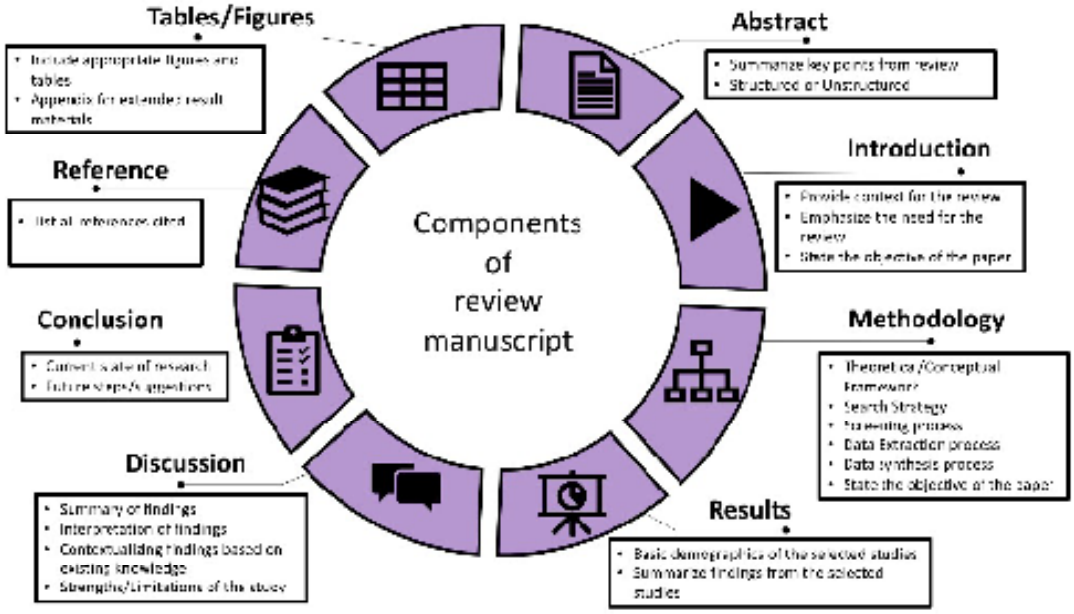

Figure 5 Components of a review manuscript

PRISMA Statement

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement is a combination of a checklist and a flow diagram that standardizes the reporting of reviews so that all the necessary steps are transparent, complete, and accurate (Page et al., 2021). This helps the authors to report about why the review was done, what they did, and what they found consistently. Using the PRISMA checklist and flow diagram ensures the methodological quality of the review, allows readers to assess strengths and weaknesses, and permits replication of review methods (Guelph-Humber Library Services, 2021). Nowadays a lot of journals require the researchers to complete a PRISMA checklist and flow diagram when they submit their reviews for publication. For different types of reviews, there are different versions of PRISMA checklists (Sarkis-Onofre et al., 2021). But the flow diagram is similar to all types of reviews (Page et al., 2021). The flow diagram depicts the flow of search and screening through the different phases of a review. It maps out the number of records identified, included, and excluded, and the reasons for exclusions. A sample flow diagram is shown in Figure 6.

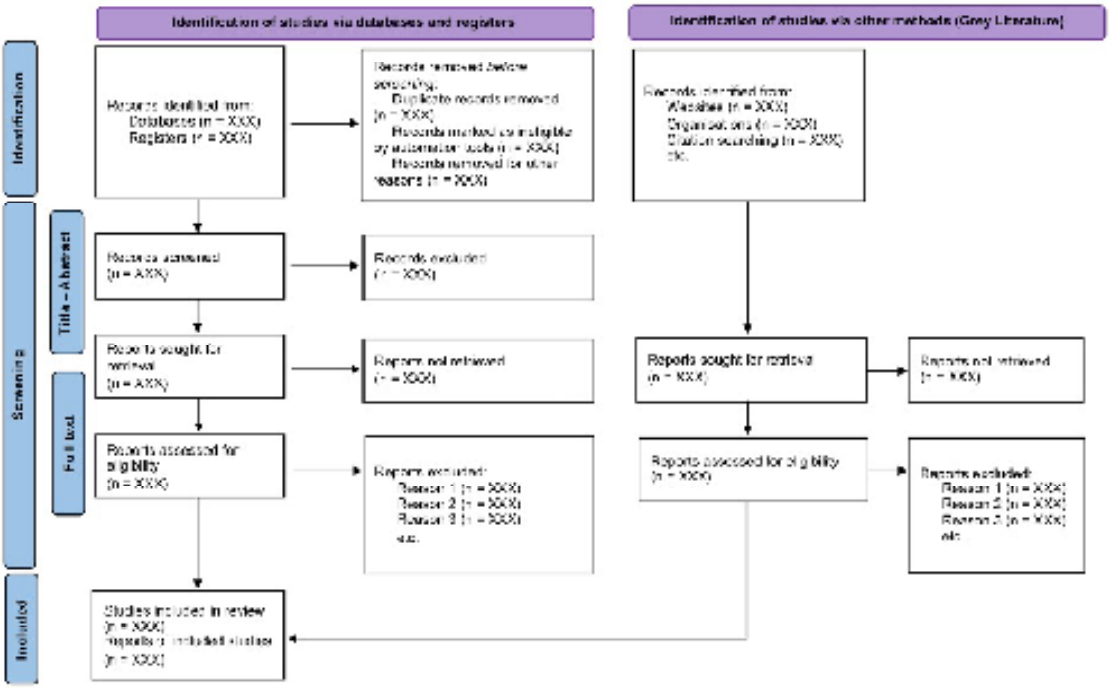

Figure 6 A sample of a flow diagram showing the components of records identified, included, and excluded, and the reasons for exclusions, finally selected paper numbers

Review Team: Roles and Responsibilities

A successful review requires a team that has variable skill sets that are necessary for the review to come to fruition. Therefore, investigators need to assemble a team that can efficiently handle the different demands of conducting a review article. Minimally, at least two investigators with proficiency in knowledge synthesis methodology and the ability to direct content are needed in the review team. Moreover, a librarian is a useful member that can be added to this team to conduct the comprehensive and expansive systematic search. The team is also responsible for dictating the scope of capture (breadth and depth) of information for the knowledge synthesis and also the potential strengths and limitations of the paper. Figure 7 illustrates these roles and responsibilities.

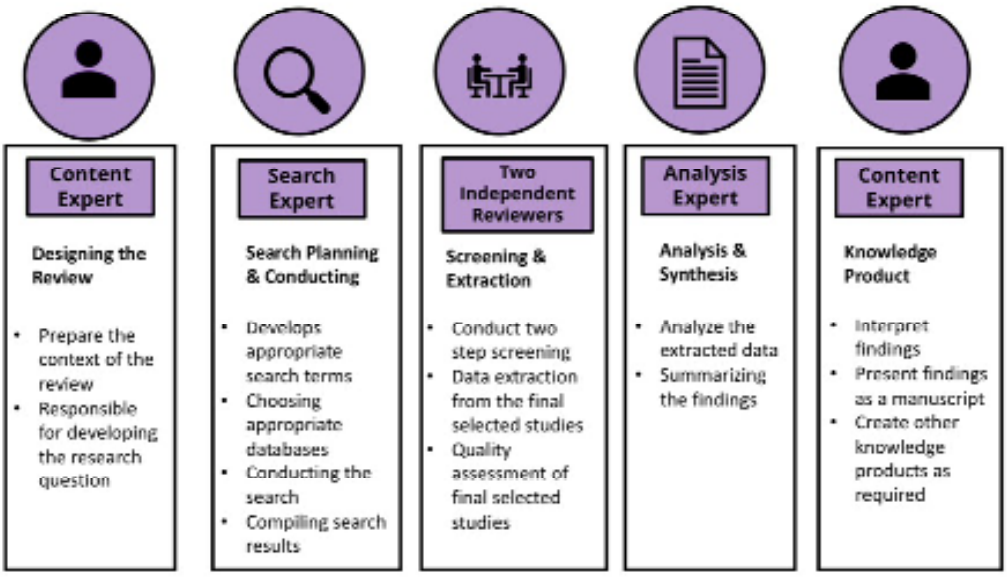

Figure 7 Review team: roles and responsibilities

Software for Assisting Reviews

Conducting reviews in a lot of instances has become a huge undertaking. The sheer number of articles to screen, keeping track of the two-person screening, or keeping notes of several articles identified and processed from different sources – all need careful execution and recording. There are some software or applications which make the management of conducting reviews easier. Some of them are commercial and some of them are open-sourced, which come with limited capabilities. For example, COVIDENCE is software that requires a paid subscription (https://www.covidence.org/). Also, Rayyan is a software and it offers free service (https://www.rayyan.ai/). This software has the potential to reduce the time and effort needed to conduct a literature review drastically by streamlining the review process and through automated documentation.

CONCLUSION

In this manuscript, we summarized a review conducting process and discussed different types of reviews that can be undertaken to fulfil knowledge synthesis requirements. A review can summarise the current understanding so that we can identify the research gap. Reviews can also be used for an in-depth understanding of measures of disease burden or measures of exposure-outcome association. Developing skills for conducting the review is an important skill for any researcher, academic group, as well as institution.

CONFLICT OF INTEREST

The authors declare that they have no competing interests in publishing this article.

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MINI REVIEW

Immune System in COVID-19: Is It Temporarily Defeated While Conquering?

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ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is spreading worldwide and becomes a major cause of mortality. In addition to major pathology in lungs such as pneumonia or respiratory failure, multiorgan failure and frequently haematological disorders such as thromboembolic manifestations are leading causes of mortality. This study reviews the interaction of the immune system with target cells, the role of cytokines and other components such as complements encountered in the pathophysiology of major disease processes and possible post-recovery complications. Although there are some clinical effects induced by strong immune reactions, long term immunity against the virus is found in the majority.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection imposes a major health problem in recent years and many people are affected socioeconomically. Coronaviruses belong to the family *Coronaviridae* which are RNA viruses. The virus is transmitted to humans mainly through the inhalation of droplets or aerosols and contact with contaminated surfaces. Viruses primarily affect the respiratory system ranging from mild infection to acute respiratory distress syndrome (ARDS) and multiple organs failure. Haematological disorders such as thrombosis contribute significantly to unfavourable prognosis in severely ill patients. These pathophysiologic reactions are

mediated by effector immune cells, cytokines including chemokines, complement system and sometimes these immune reactions can trigger serious pathologic complications in the body of the patients.

Cytokine Storm and Thrombosis

The occurrence of widespread macro and micro thrombosis is strongly associated with a grave outcome. The SARS-CoV-2 virus enters target cells by binding to angiotensin-converting enzyme-2 (ACE-2) receptors in the respiratory epithelium followed by endocytosis and replication. Subsequently, immune cells mainly macrophages are activated to produce cytokines including chemokines. A genome-wide association study (GWAS) revealed an association between the disease severity and ABO genes, SLC6A20, LZTFL1, CCR9, FYCO1, CXCR6 and XCR1 in chromosome 3p21.31 in patients with severe COVID-19 (Ellinghaus et al., 2020).

Interleukin (IL)-6, IL-1B, IL-12 and tumour necrosis factor-α (TNF–α) are important cytokines involved in the pathogenesis of COVID-19. Excessive production of these cytokines during exposure to viral infection may create a cytokine storm causing severe pneumonia as well as systemic hyper-inflammation and multiple organ involvement. Various immune cells, lymphocytes and macrophages, are involved in this cytokine storm syndrome and it is also called macrophage activation syndrome (MAI) (McGonagle et al., 2020). TNF–α and IL-1 initiate the tissue factor production from macrophages which can activate the coagulation cascade and IL-1 and IL-6 activate the plasminogen activator inhibitor. A high level of IL-6 is a poor prognostic marker in predicting the clinical outcome of infection (Witkowski et al., 2016). It can be explained by the fact that IL-6 suppresses NK cell cytolytic function and subsequently prolong the interaction between innate and adaptive immune cells that further promotes cytokine storm, hemophagocytosis, and multi-organ dysfunction. Injured and dying cells produce damage-associated molecular patterns (DAMP), mainly high mobility group box-1 (HMGB-1) that initiates and perpetuates a powerful immune response producing proinflammatory cytokines (Cicco et al., 2020).

There is a possible role of lupus anticoagulants which is linked to proinflammatory state and hypercoagulability in COVID-19 although their significance is unclear. Antiphospholipid antibodies bind to endothelium and monocytes and these factors stimulate to express adhesion molecules which facilitate platelet adhesion, platelet activation and increased phospholipid of glycoprotein IIB-IIIa (Tung et al., 2021). Viruses can cause damage to the endothelium contributing to the release of tissue factors from subendothelial cells for the initiation of the coagulation cascade (Tung et al., 2021). Tissue factor also activates the extrinsic pathway of coagulation and increase the risk of venous thromboembolism (VTE) (Terpos et al., 2020).

Human *in vitro* models of COVID-19 showed infected monocytes with a hyperexpression of procoagulant genes including fibrinogen, serine protease inhibitors (SERPINS), tissue factor, and factors II and X which induce coagulopathy (Giannis et al., 2020). Complement activation induced by infection results in the release of proinflammatory cytokines and microvascular damage (Diurno et al., 2020).

Immuno-Thrombosis and Venous Thromboembolism

Endothelial dysfunction is the basis of COVID-19 associated coagulopathy (CAC) dysfunction (Huertas et al., 2020). In an observational study of the clinical outcome of COVID-19 patients, a poor outcome is seen in patients with hypertension and diabetes which are associated with endothelial

dysfunction compared to those without these comorbidities (Huertas et al., 2020). Endothelial disruption enhances platelet activation and aggregation with the formation of a plug which acts as a template for adhesion of coagulation factors.

Hypoxia which is a common manifestation of COVID-19 patients induces endothelial dysfunction and hypercoagulability. Hypoxia caused by severe COVID-19 pneumonia induces the expression of hypoxia-induced factors (HIFs) which are transcription factors expressed by vascular endothelium and immune cells (Palazon et al., 2014). HIFs together with cytokine TNF-α upregulate the tissue factor expression and promote the release of plasminogen activator inhibitor-1 (PAI-1) which inhibits tissue plasminogen activator (tPA) reducing the activity of plasmin consequently triggers thrombosis (Loo et al., 2021). Markers of sepsis-induced coagulopathy (SIC) such as prolonged prothrombin time (PT), increased fibrinogen and increased d-dimers are seen in 21.6% of patients (Price et al., 2020; Tang et al., 2020; Wang et al., 2021). The release of proinflammatory cytokines mainly IL-6 and cathepsin G, a serine protease, cause platelets activation and aggregation (Bautista et al., 2021).

Complement activation plays a major role in triggering thrombosis. The final complement complexes C5b-9 resulted from the activation and cleavage of the complement proteins act as a membrane attack complex. It can attack the target cells causing lysis of cells which increases the procoagulant activity (Wiedmer et al., 1986). C3b fragment of complement binds to CR1 receptor on platelet membranes triggering the release of short-chain polyphosphate (polyP) from platelets, which induces the expression of TF. Complement component C5a may also contribute to the recruitment of neutrophils (Loo et al., 2021).

Previous studies revealed that there was a high risk of VTE in 35-85% of COVID-19 inpatients compared to the overall risk of 2% in hospitalized patients in the general medical ward. A vascular filling defect on computed tomography pulmonary angiography (CTPA) may require a differential diagnosis of immune-thrombosis or local pulmonary thrombosis or classic pulmonary embolism (Klok et al., 2020). Incidence of formation of blood clots in leg veins, deep vein thrombosis (DVT) was slightly lower than pulmonary thrombosis and microthrombi were frequently seen in pulmonary capillaries (Ackerman et al., 2020; Klok et al., 2020; Longchamp et al., 2020).

Neutrophil Extracellular Traps and Thrombosis

Neutrophils play the first line of defence in acute inflammation. They act as antigen-presenting cells (APC) presenting the virus to immune effector cells such as T lymphocytes. Elevated neutrophils to lymphocyte ratio (NLR) and very low lymphocyte counts are common findings in severe COVID-19 patients. NLR is a poor prognostic marker in COVID-19 infected cases (Wang et al., 2021; Rangel et al., 2020). NETosis is a process in which neutrophil extracellular traps (NETs) are formed by neutrophil DNA materials that form networks with extracellular fibres to bind to pathogens and trap them. The role of NETosis in viral infection has been described (Jenne et al., 2013). When neutrophils are stimulated by viruses, toxins or proinflammatory cytokines such as TNF and IL-8, the nuclear membrane disintegrates and release chromatin material from the nucleus which is mixed with proteins of neutrophilic granules in the cytoplasm. After hypercitrullination of nuclear histones, DNA-protein complexes (NETs) are released into the extracellular spaces. Uncontrolled production of NETs is associated with diseases gravity and the extent of lung injury (Bendib et al., 2019). Histones, the major component of NETs, attract, activate and aggregate platelets which will lead to thrombosis. Tissue

factor is induced by activated platelets and trigger coagulation cascade augmenting the thrombus formation. Neutrophils also promote coagulation by releasing an enzyme, neutrophil elastase, which cleaves the tissue factor pathway inhibitor (TFPI) contributing to thrombosis (Loo et al., 2021).

Evidence of NETosis-related microthrombotic events have been seen in COVID-19 autopsied cases (Borges et al., 2020; Parra-Medina et al., 2021). Tracheal aspirate and plasma of COVID-19 patients show increased NET level, neutrophil-platelet aggregates and increased plasma MPO-DNA complexes show elevated NET that is associated with immunothrombosis and ARDS. The significant level of NETS induces heparin-induced thrombocytopenia and platelet/lymphocyte ratio is a poor prognostic factor (Zhou et al., 2020). Studies have shown that NETs entrap viruses by a DNA web. However, NET-induced hyper-inflammation and thrombosis are unwanted events leading to the poor clinical outcome (Funchal et al., 2015).

Pulmonary embolism and deep venous thrombosis are the most frequent thromboembolic attacks in 20 – 30% of severe cases (Grimes et al., 2020; Connors et al., 2020). A thrombus may form in other organs such as cerebral circulation arterial and venous, coronary, mesenteric and peripheral arteries. Microvascular inflammation per se can cause acro-ischaemia (COVID-toes). Thromboinflammation plays an essential role in ARDS and determines the prognosis of severe cases. Platelets are also involved in the infectious process by triggering inflammation and thrombosis. When the platelet-toll-like receptors 2 (TLR-2) are activated there is cross-link formation between platelets and neutrophils. Activation of the tissue factor pathway of the coagulation cascade leads to the formation of thrombi in the microvasculature, subsequently resulting in total consumption of platelets and procoagulant factors, with the result of haemorrhage. Immuno-thrombotic events present with laboratory findings are distinct from DIC criteria. An elevated D-dimer at admission (≥ 20 mg/L) and constant rise in D-dimer are associated with increasing severity and in-hospital mortality (Yao et al., 2020; Zhoau et al., 2020).

Macrophage Activation Syndrome and Acute Respiratory Distress

Features of macrophage activation syndrome (MAS) such as increased levels of cytokines namely IL-2, IL-7, TNF–α and serum ferritin have been observed in severe COVID-19 pneumonia (Huang et al., 2020). Hyperferritinemia, the marker of extensive macrophage activation, is a hallmark of COVID-19 pneumonia (Otsuka et al., 2020). MAS typically show signs of disseminated intravascular coagulation such as reduced fibrinogen, reduced platelets and increased d-dimers. High D-dimer was found in COVID-19 patients (McGonagle et al., 2020; Tang et al., 2020). MAS like hyper-inflammation plays an important role in the pathogenesis of severe pneumonia and ARDS. Approximately 20% to 40% of patients develop ARDS in the course of pneumonia (Huang et al., 2020, Wu et al., 2020).

Cell pyroptosis, a type of cell death, mediated by an activated cascade of NLRP-3 inflammasome was seen in COVID-19 associated lung inflammation (Hoffmann et al., 2020). High levels of cleaved gasderrmine D (GSDMD), a pore-forming protein, which is a trigger of pyroptosis has been commonly observed in the lungs of severe COVID-19 patients compared to controls (Zhang et al., 2021). Alveolar macrophages are major cells that are highly positive for GSDMD staining on multiplex immunohistochemistry. The inflammation associated with cell death activates macrophages to produce pro-inflammatory cytokines and recruit T cells to the site. In addition, the entry of viral RNA into macrophages may directly activate them to produce cytokines (Malmgaard, 2004). Immune-mediated injury to parenchymal

and endothelial cells forms the tissue debris together with leaking from the newly formed capillaries (capillary leak syndrome) (Matthay et al., 2011), contributing to the formation of hyaline membranes in alveoli leading to insufficient oxygenation of capillary blood and ARDS (Bahloul et al., 2021). COVID-19 associated hypoxemia stimulates expression of hypoxia-inducible factors (HIFs) that activate macrophages to aggregate locally and express pro-inflammatory cytokines while HIF-1α enhances complement-mediated endothelial damage (Palazon et al., 2014).

Renin-Angiotensin-Aldosterone System Dysregulation and Hypercoagulability

Angiotensin-converting enzyme 2 (ACE2) is highly expressed in kidneys, heart, pancreas, liver, small intestine, neurons and blood vessels. Autopsies of COVID-19 patients showed multisystem injuries, including acute lung injury, acute renal injury, cardiac injury, liver dysfunction and pneumothorax (Yang et al., 2020). The SARS-CoV-2 virus binds to ACE2 receptors which mediate the entry of the virus into the target cell. Upon binding, the transmembrane serine protease (TMPRSS2) cleaves ACE2 to promote viral uptake and metallopeptidase domain 17 (ADAM17) then cleaves ACE2 to cause ectodomain shedding (Heurich et al., 2014). The resultant ACE 2 downregulation disturbs the formation of angiotensin (Ang). Consequently, it will change the absolute level of Ang-II and increase the ratio of Ang II to Ang-(1-7). Increased Ang II level augments its effect on proinflammatory and prothrombotic processes. Ang II also activates the angiotensin type 1 receptor (AT1R) which enhances platelet activation and impairs fibrinolysis, resulting in hypercoagulability (Guo et al., 2001; Ni et al., 2020; Remkova et al., 2010).

The possibility of endothelial cell activation/damage due to the virus binding to ACE2 receptor may further increase VTE risk.

Post-acute COVID-19 Complications

In the early recovery phase of COVID-19 illness, some patients experience complications. It is important to achieve early diagnosis and effective management to ensure a favourable outcome. Persistent hypoxemia due to restrictive diffusion as a result of pulmonary fibrosis with dyspnea is the most common sequelae. Resolution of acute renal injury during acute COVID-19 occurs in the majority of patients. However, a reduced estimated glomerular filtration rate (eGFR) has been reported at a 6-month follow-up (Nalbandian et al., 2021). Neuro-psychiatric manifestations such as anxiety, sleep disturbance and post-traumatic stress are common and early rehabilitation care and counselling are important for those cases. As the duration of the hyper-inflammatory state is unknown, there may be continuing risk of developing thromboembolic problems such as pulmonary embolism, intracardiac thrombus, thrombosed arteriovenous fistula and ischaemic stroke (Patell et al., 2020). Effects on the cardiovascular system such as myocardial fibrosis can result in cardiomyopathy or arrhythmia. Autonomic dysfunction occurs after a viral illness, resulting in postural orthostatic tachycardia syndrome and inappropriate sinus tachycardia (Yao et al., 2020). Studies showed that biomarkers of cerebral injury, such as elevated peripheral blood levels of neurofilament light chain have been found in patients with COVID-19 (Ameres et al., 2020). COVID-19 related secondary hemophagocytic lymphohistiocytosis (HLH) is a haematological disorder affecting hemopoietic tissues such as bone marrow, spleen, liver and lymph nodes. It is associated with fever, splenomegaly, cytopenia, hypofibrinogenemia, low or absence of natural killer (NK) cell activity and hyperferritinemia (Henter et al., 2007). The HLH syndrome can be seen as a result of dysregulated immune reactions after COVID-19 infection in patients during the recovery phase (Henter et al., 2007; Naous et al., 2021).

Treatment of COVID-19

Understanding the immnuopathophysiology of COVID-19 effects, several attempts have been in trial for treatment. Monoclonal antibodies were used to block the receptor of IL-6 to slow down the cytokine hyperproduction (Zhang et al., 2021). In a study, Eculicumab acts to antagonize the complement C5 in which cases showed decreased inflammatory markers such as CRP and improved patient recovery (Diurno et al., 2020). An experimental study aimed to inhibit DAMP, monoclonal antibodies to HMGB, together with antineuramidase inhibitor revealed effective therapy (Hatayama et al., 2019). As SARS-CoV-2 uses ACE-2 receptor for entry into cells, human recombinant soluble ACE2 antibodies (hrsACE2) is found to be a promising treatment for severe infection (Zoufaly et al., 2020). Convalescent SARS serum samples can neutralize spike-driven virus entry showing that vaccine targeting spike proteins have promising benefits in prevention. As we have mentioned before, NETs are the main contributors to pathogenetic effects, thus, using drugs that can disrupt neutrophil activation and NETs formation are hopeful strategy (Hoffmann et al., 2020). Studies have shown that a better outcome was observed with anticoagulant and antiplatelet therapy for severe clinical cases with features of coagulopathy and those requiring mechanical ventilation (Godino et al., 2021).

CONCLUSION

The human immune system and immune cells fight against any challenging infection. The cytokines including chemokines produced by activated immune cells to recruit inflammatory immune cells at the site of injury aided by the complement system to enhance the protective effects. During the process of attempting to defend against COVID-19 infection, the powerful cytokine storm and hyperactive complement-mediated reaction result in some unwanted side reactions such as immunothrombosis and hyper-inflammatory reactions. Understanding these pathophysiological processes leading to hyperactive immune status will guide the clinicians to plan more effective management. Recent development in treatment remedies is in progress to modify these immune dysregulations so that better control of immune dysregulation can be achieved.

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ORIGINAL ARTICLE

Occupational Risk Factors for Seropositive Leptospirosis among Town Service Workers in Northeastern Malaysia

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ABSTRACT

Leptospirosis is speculated to be one of the most prevalent re-emerging zoonotic diseases to date, and town service workers are continuously exposed to occupational hazards that may increase their risk of infection. This study aimed to determine the occupational risk factors for leptospirosis among town service workers in northeastern Malaysia. A cross-sectional study was conducted among town service workers from four municipal councils. All sera samples were tested for the presence of anti-leptospiral antibodies using an enzyme-linked immunosorbent assay (ELISA) followed by a microscopic agglutination test (MAT). We found that 82 serum samples from 321 respondents were positive in the MAT (seroprevalence rate of 25.5%). Multiple logistic regression analysis identified overtime work (adj. OR 2.13; 95% CI 1.19, 3.84), contact with animals while working (adj. OR 2.09; 95% CI 1.06, 4.11), sighting of rats at the worksite (adj. OR 2.17; 95% CI 1.11, 4.25) and living less than 200 m from a river (adj. OR 1.84; 95% CI 1.03, 3.28) as risk factors for leptospiral infection. Whereas age (adj. OR 0.95; 95% CI 0.93, 0.98), wearing boots while working (adj. OR 0.44; 95% CI 0.25, 0.80) and washing hands with soap after work (adj. OR 0.20; 95% CI 0.10, 0.42) were recognised as protective factors. In conclusion, an association was observed between leptospirosis seropositivity among town service workers and the occupational factors. Prevention and control strategies for leptospirosis will require more focus on curbing the possible sources of leptospirosis transmission and maintaining safe work practices in high-risk working environments.

INTRODUCTION

Human leptospirosis is a re-emerging endemic infectious disease in Malaysia (Thayaparan et al., 2013) and it is well known as an occupational disease for many groups of workers who are involved in outdoor work or work that requires contact with animals (Cointreau, 2006; Spies, 2010). Areas such as the garbage disposal sites of public authorities, open dumps and illegal dumping sites with uncollected solid waste contribute to a favourable environment for rodents to breed and feed while spreading leptospirosis via excreted urine (Cointreau, 2006; Spies, 2010).

Leptospirosis is still under-reported due to the wide range of clinical presentations associated with acute leptospiral infection (Levett, 2001; Victoriano et al., 2009). In Malaysia, Ministry of Health data showed that from 2004 to 2009, the prevalence of leptospirosis increased dramatically and that the case fatality rates (CFR) varied from 1.8% to 7.6%, with an average of 4.44% (Ministry of Health, 2011; Thayaparan et al., 2013).

The incubation period for leptospirosis is usually between 5 and 14 days, with a range of 2 to 30 days. In humans, it can cause a variety of symptoms, from asymptomatic to mild (influenza-like symptoms) to severe (Weils' syndrome) clinical manifestations. Delay in seeking treatment leads to complications such as renal failure, meningitis (inflammation of the membrane around the brain and spinal cord), liver damage, respiratory distress and widespread haemorrhage (Dircio Montes Sergio et al., 2012).

Humans are exposed to leptospirosis via occupational, recreational or environmental factors (Levett, 2001). High-risk occupations, such as town service workers, paddy planters, army personnel and health care workers, are more vulnerable to leptospiral infection due to the presence of occupational and environmental determinants for human leptospirosis in the workplace (Mohd Ridzuan et al., 2016; Sulong et al., 2011).

There are four job categories for town service workers: garbage collector, town cleaner, landscaper and lorry driver/mechanic. Garbage collectors collect garbage from containers or waste bins located in residential, commercial and industrial areas before dumping the waste material onto a lorry (truck) for disposal at landfills. Town cleaners' duties include sweeping, collecting and removing litter, detritus and leaves from public spaces (i.e., roads, pavements, drains, wet markets and public precincts). Landscapers perform a range of duties, including transporting, planting, mulching, fertilizing and watering vegetation. They also cut and trim grass via manual labour or the use of power-operated equipment. Lorry drivers drive the garbage collection lorries from the collection sites to the landfill sites, and sometimes they assist garbage collectors in performing their job. Whereas a lorry mechanic's job includes maintenance (including washing) and repair of garbage collection lorries.

Town service workers are susceptible to leptospirosis due to their substantial involvement in every step of the waste management process. In fact, a country-wide study conducted in Denmark found that infectious disease and injury risks for solid waste workers are six times higher than those of control baseline populations (Cointreau, 2006).

Leptospirosis is preventable if appropriate measures are taken, especially for modifiable risk factors. Intervention among high-risk groups is one of many preventive measures that could be taken to control this disease (Zavitsanou & Babatsikou, 2008). Thus, this study was conducted to determine the occupational factors for leptospirosis among town service workers in northeastern Malaysia.

MATERIALS AND METHODS

Study Design and Population

A cross-sectional study was performed in four districts in northeastern Malaysia involving 321 town service workers from the Municipal Council and three District Councils. The Municipal Council provides public services within its area of jurisdiction, which is 116 km^2, whereas each District Council provides public services in an operational area of about 50 km^2.

The sample size was calculated based on the 24.7% seropositivity for leptospirosis among town service workers (Sulong et al., 2011) at a 95% confidence interval (CI). After considering a dropout rate of 20%, the estimated sample size required for the study was calculated to be 346. The sampling frame was based on the list of town service workers provided by the Municipal Council and three District Councils (denoted District A, District B and District C) who fulfilled the study criteria. It included workers in the four job categories previously mentioned who had been working in the department for more than six months. Office workers and workers who were absent or on leave during the study period were excluded from the study. Proportionate sampling was conducted to determine the number of respondents that needed to be selected from each district. Simple random sampling was used to select respondents from the list.

Blood Samples and Serologic Tests

A venous blood sample (5 mL) was obtained from each respondent and the serum was separated and stored at −20°C. All sera samples were tested for the presence of anti-leptospiral antibodies using an enzyme-linked immunosorbent assay (ELISA) and microscopic agglutination test (MAT) following standard methods (WHO, 2007).

Live *Leptospira* cell suspensions were added to serially diluted serum samples in microtitre plates and incubated at 30°C for 2 h. Agglutination was examined using dark field microscopy at a magnification of ×100. Agglutination was considered to be positive agglutinations when the approximate number of free leptospires was <50% than the number of leptospires in the control wells. The titre result was taken as the last dilution that showed <50% of free leptospires compared to control wells. A seropositive leptospirosis respondent was defined as a person who had a MAT titre of 1 ≥ 100 (Plank & Dean, 2000).

RESULTS

Of the 346 workers who were eligible for this study, 321 participated, resulting in a response rate of 92.8%. All respondents were of Malay ethnicity. The mean age was 40.6 (10.28) years and the mean duration of employment was 12.1 (9.62) years. Table 1 shows the sociodemographic characteristics of the town service workers. Among the 321 respondents, 82 serum samples returned a positive MAT result, giving a leptospirosis seroprevalence rate of 25.5%.

Table 1 Sociodemographic characteristics of town service workers (*n* = 321)

Variable	Frequency (%)	Mean (SD)
Age (year)		40.6 (10.28)
Gender		
Male	309 (96.3)	
Female	12 (3.7)	
Marital status		
Married	268 (83.5)	
Single	44 (13.7)	
Widower	9 (2.8)	
Number of children		3.7 (2.49)
Monthly income (RM)		1198.14 (419.35)
Education level		
No formal education	4 (1.2)	
Primary school	64 (19.9)	
Lower secondary school	88 (27.4)	
	151 (47.0)	
Upper secondary school	14 (4.4)	
Form 6 / Diploma		
Town council		
Municipal Council	183 (57.0)	
District A	48 (15.0)	
District B	49 (15.3)	
District C	41 (12.8)	
Job category		
Town cleaner	157 (48.9)	
Lorry driver/ mechanic	71 (22.1)	
	56 (17.4)	
Landscaper	37 (11.5)	
Garbage collector		

Table 2 shows that three socio-demographic, nine occupational and three environmental and household factors were associated with leptospirosis. No recreational activities were associated with leptospirosis seropositivity. Moderate knowledge and unsatisfactory practices were associated with an increased risk of leptospiral infection.

Table 2 Univariable analysis of associated factors for leptospirosis among 321 town service workers in northeastern state using simple logistic regression

Variable	Seropositive n = 82	Seronegative n = 239	Crude OR[a]	95% CI[b]	*P* value[e]
	Freq. (%)	Freq. (%)			
Socio-demographic Factors					
Age (year)	37.6 (10.57)*	41.7 (9.99)*	0.96	0.94, 0.99	0.002
Gender (Male)[a]	77 (93.9)	32 (97.1)	0.47	0.14, 1.51	0.202
Marital status (Single/Widower)[b]	21 (25.6)	32 (13.4)	2.23	1.20, 4.14	0.011
No of children	3.5 (2.36)*	3.7 (2.53)*	0.96	0.85, 1.07	0.454
Income (RM)	1115 (375)*	1226 (430)*	0.99	0.99, 1.00	0.041
Level of education (≥ Upper secondary)[c]	45 (54.9)	120 (50.2)	1.21	0.73, 1.99	0.466
Occupational Factors					
Duration of employment (year)	10.0 (8.24)*	12.8 (9.97)*	0.97	0.94, 0.99	0.026
Average work per week (6 or 7 days)[d]	43 (52.4)	87 (36.4)	1.93	1.16, 3.20	0.011
PPE used during work (yes)[e]					
Boots	33 (40.2)	147 (61.5)	0.42	0.25, 0.70	0.001
Long sleeve shirt	66 (80.5)	194 (81.2)	0.96	0.51, 1.81	0.892
Rubber gloves	28 (34.1)	76 (31.8)	1.11	0.65, 1.89	0.695
Mask	8 (9.8)	49 (20.5)	0.42	0.19, 0.93	0.032

Presence of wound during work (yes)[e]					
Hands	29 (35.4)	53 (22.2)	2.08	0.70, 6.15	0.186
Leg	8 (9.8)	17 (7.1)	0.99	0.38, 2.60	0.993
Other parts	5 (6.1)	15 (6.3)	0.66	0.22, 1.98	0.454
Wash hands with soap after work (yes)[e]	54 (65.9)	216 (90.4)	0.21	0.11, 0.38	<0.001
Shower after work (yes)[e]	79 (96.3)	228 (95.4)	1.27	0.35, 4.67	0.719
Eat or drink while working (yes)[e]	50 (61.0)	103 (43.1)	2.06	1.24, 3.44	0.006
Smoking while working (yes)[e]	35 (42.7)	58 (24.3)	3.86	1.76, 8.49	0.001
Contact with animal during working hour (yes)[e]	26 (31.7)	35 (14.6)	2.71	1.50, 4.87	0.001
Sighting rats/rodents at work site (yes)[e]	65 (79.3)	140 (58.6)	2.70	1.50, 4.89	0.001
Environmental Factors					
House status (Rent)[f]	19 (23.2)	57 (23.8)	0.96	0.53, 1.74	0.901
Type of house					
Brick	28 (34.1)	86 (36.0)	1	-	0.313
Wood	30 (36.6)	67 (28.0)	1.38	0.75, 2.52	0.303
Mixed	24 (29.3)	86 (36.0)	0.86	0.46, 1.60	0.627
Main water source (Open / Tube well)[g]	30 (36.6)	83 (34.7)	1.08	0.64, 1.83	0.761
Type of toilet (Pour)[h]	44 (53.7)	107 (44.8)	1.43	0.86, 2.36	0.165
Distance from house to river (≤200 metres)[i]	37 (45.1)	77 (32.2)	1.73	1.04, 2.89	0.036
Distance from house to paddy field (≤200 metres)[i]	25 (30.5)	54 (22.6)	1.50	0.86, 2.63	0.154
Household animal ownership (yes)[e]					
Cats	32 (39.0)	91 (38.1)	0.88	0.35, 2.19	0.782
Cow	16 (19.5)	23 (9.6)	2.55	1.17, 5.57	0.019
Buffalo	0	2 (0.8)	0	0	0.999
Goat	11 (13.4)	21 (8.8)	1.63	0.70, 3.77	0.257
Horse	1 (1.2)	4 (1.7)	0.69	0.07, 6.33	0.739
Neighbour's animal ownership (yes)[e]					
Cats	45 (54.9)	124 (51.9)	0.95	0.39, 2.30	0.914
Cow	21 (25.6)	40 (16.7)	1.72	0.89, 3.33	0.106
Buffalo	1 (1.2)	6 (2.5)	0.45	0.05, 3.79	0.459
Goat	17 (20.7)	41 (17.2)	1.20	0.61, 2.37	0.603
Horse	2 (2.4)	7 (2.9)	0.77	0.16, 3.84	0.753
Presence of rodent/ rat in house (yes)[e]	69 (84.1)	175 (73.2)	1.94	1.01, 3.75	0.048
House area affected by flood (yes)[e]	30 (36.6)	84 (35.1)	1.07	0.63, 1.79	0.814
Accumulate garbage nearby house (yes)[e]	51 (62.2)	131 (54.8)	1.36	0.81, 2.27	0.245
Garbage disposal (Buried/Open burning/ Others)[j]	44 (53.7)	109 (45.6)	1.38	0.84, 2.28	0.209

Reference group; [a]female, [b]married, [c]lower secondary, [d]work 5 days per week, [e]no, [f]owned, [g]treated pipe water, [h]flush, [i]>200meters, [j]public service, [k]satisfactory (≥75%)
OR = Odds ratio, CI = Confidence Interval, RM = Ringgit Malaysia, PPE = Personal Protective Equipment
[*]Mean (SD)

Table 2 cont.

Variable	Seropositive n = 82 Freq. (%)	Seronegative n = 239 Freq. (%)	Crude OR[a]	95% CI[b]	P value[e]
Recreational activities (yes)[e]					
Canoeing	1 (1.2)	9 (3.8)	0.32	0.04, 2.53	0.277
Camping	7 (8.5)	10 (4.2)	2.14	0.79, 5.81	0.137
Horse riding	6 (7.3)	8 (3.3)	2.28	0.77, 6.78	0.138
Gardening	43 (52.4)	122 (51.0)	1.06	0.64, 1.75	0.828
Swimming	6 (7.3)	21 (8.8)	0.82	0.32, 2.11	0.680
Fishing	29 (35.4)	68 (28.5)	1.38	0.81, 2.34	0.240
Worker's knowledge, attitude and practice					
Worker's knowledge					
Good (≥72%)	20 (24.4)	86 (36.0)	1	-	0.105
Moderate (<72%)	49 (59.8)	112 (46.9)	1.88	1.04, 3.40	0.036
Poor (Never heard)	13 (15.9)	41 (17.2)	1.36	0.62, 3.01	0.443
Worker's attitude (Unsatisfactory (<75%))[k]	47 (57.3)	107 (44.8)	1.66	0.99, 2.75	0.051
Worker's practice (Unsatisfactory (<75%))[k]	61 (74.4)	132 (55.2)	2.36	1.35, 4.11	0.003

Reference group; [a]female, [b]married, [c]lower secondary, [d]work 5 days per week, [e]no, [f]owned, [g]treated pipe water, [h]flush, [i]>200meters, [j]public service, [k]satisfactory (≥75%)
OR = Odds ratio, CI = Confidence Interval, RM = Ringgit Malaysia, PPE = Personal Protective Equipment
[*]Mean (SD)

As shown in Table 3, there were seven associated risk factors for leptospiral infection, including working overtime, contact with animals while working, sighting of rats at the worksite and living ≤200 m from a river. Older age, wearing boots while working and washing hands with soap after work were identified as protective factors for leptospirosis. It was found that recreational activities and workers' knowledge, attitudes and practices were not significantly associated with leptospirosis.

Table 3 Associated factors for seropositive leptospirosis among 321 town service workers using multiple logistic regression

Variable	Adjusted OR[a]	95% CI[b]	*p*-value
Age (year)	0.95	0.93, 0.98	0.001
Working overtime during the weekend No Yes	1 2.13	1.19, 3.84	0.011
Wearing boots during work No Yes	1 0.44	0.25, 0.80	0.007
Wash hands with soap after work No Yes	1 0.20	0.10, 0.42	<0.001
Contact with animals during working hours No Yes	1 2.09	1.06, 4.11	0.033
Sighting rats/ rodents at the worksite No Yes	1 2.17	1.11, 4.25	0.024
≤200 metres from the house to the river No Yes	1 1.84	1.03, 3.28	0.039

[a]OR = Odds Ratio, [b]CI = Confidence Interval
Hosmer and Lemeshow Test *p*-value = 0.830
Classification table overall percentage correct = 79.4%
Area under ROC curve = 78.3%
No multicollinearity

DISCUSSION

In this study, age was the only socio-demographic factor associated with seropositive leptospirosis and the only independent numerical variable associated with leptospiral infection. The mean age of the respondents was 40.6 (10.28) years, with a range of 20 – 68 years. Interestingly, multiple logistic regression analyses showed that an increase in age of one year resulted in a 0.95 odds reduction of being seropositive for leptospirosis. A possible explanation is that as workers get older, they become more familiar with safe practices, within and outside of work. Workers were found to gain such knowledge through formal and informal education from employers, supervisors, friends or other sources, thus increasing their awareness of the health risks imposed by their daily work and personal activities. A similar finding is also reported by a study conducted in the Federated States of Micronesia (Colt et al., 2014).

In contrast, a cross-sectional study with 280 respondents from a rural area in Khuzestan, southwest Iran, reported that age was significantly associated with leptospiral infection. A higher infection rate was observed in those older than 35 years. The author mentioned that it was a well-known fact that young people in most of the villages in the region were not interested in doing outdoor work. They instead preferred to migrate in search of indoor work in big cities (Alavi et al., 2014). In another study, patients over 30 years old were found to have twice the risk of becoming a confirmed leptospirosis case compared to those aged ≤30 years (Adj. OR: 2.16; 95% CI: 1.05, 4.41) (Vanasco et al., 2008). Nonetheless, this was laboratory-based surveillance of suspected leptospirosis cases and not a study among asymptomatic respondents in the occupational risk group.

Despite age not being a significant factor, leptospirosis has been found to occur mainly in younger age groups in several studies. A study conducted in southern India discovered that the majority of cases were found in people aged 21 – 30 and 41 – 50 years, which is also known as the productive age group. Thus, acquiring an infection during this period could result in a momentous economic impact on the family (Kamath et al., 2014). Another study in Laos revealed that the seroprevalence of leptospirosis among younger people (15 – 34 years) was higher than that in older age groups (35–78 years). The seroprevalence ranged from 23.9% to 30.6% in the younger age group, while in the older age group, it ranged from 18.6% to 24.7% (Kawaguchi et al., 2008).

Furthermore, studies in Thailand (Phraisuwan et al., 2002) and Mexico (Leal-Castellanos et al., 2003) reported that age was not a significant factor for leptospirosis seroprevalence and that seropositivity was not seen in certain younger or older age groups. Additionally, in a study with elderly people (aged ≥60 years, and ranging from 60 to 78 years), leptospirosis was found to be associated with a severe course and higher risk for death, especially in those with an underlying co-morbidity (Gancheva, 2013).

In the present study, five occupational factors were associated with leptospirosis exposure. Three were risk factors (i.e., working overtime, contact with animals while working and sighting rats at the worksite), whereas two were protective factors (i.e., wearing boots during work and washing hands with soap after working).

A normal work schedule involves working five days a week. However, to meet the demand for various services and minimise disruption to scheduled services, workers were offered additional work (i.e., overtime) at both regular and irregular hours. In this study, about 41% of the respondents chose to work overtime over the weekend. Those who work overtime have greater exposure to and more contact with water and soil that is possibly contaminated with leptospiral-infected urine compared to those who work five days a week.

This is supported by the findings of the present study: those who worked overtime during the weekend had 2.13 times the odds of having leptospirosis compared to those who did not do overtime work during the weekend (Adj. OR: 2.13; 95% CI: 1.19, 3.84; p = 0.011).

There are many reports in the literature of prolonged exposure to and close contact with leptospiral-contaminated environments leading to an increased risk of leptospirosis (Hoenigl et al., 2014). For instance, in a study conducted in the Indian city of Surat, the risk of leptospirosis occurrence was 2.64 times higher among those who spent more than four days cleaning up after a flood than those who spent three days or less (Adj. OR = 2.64; 95% CI: 1.18 – 5.89; p < 0.05) (Bhardwaj et al., 2008). Another study conducted among adventure race participants in Florida, USA, reported that prolonged water exposure during the race was associated with an increased risk of leptospirosis (Stern et al., 2010). Prior to that, a study with Peruvian military members found that the leptospirosis infection rate was higher among recruits who stayed longer at the training site than among those who stayed for less time (Russell et al., 2003).

Wearing boots while working was identified as an independent protective predictor at the multivariable analysis level in the present study. Workers who practised wearing boots while working were less likely to have a leptospiral infection compared to those who did not wear boots while working (Adj. OR: 0.44; 95% CI 0.25, 0.80; p = 0.007). This finding emphasises the importance of compliance with personal protective equipment (PPE) rules among town service workers. Similar findings regarding the protective effect of wearing boots while working against leptospirosis have also been reported in other studies (Leal-Castellanos et al., 2003; Mohd Ridzuan et al., 2016; Sulong et al., 2011). However, a few studies have also reported no association between wearing boots and leptospirosis (Phraisuwan et al., 2002).

Other PPE usage while working, such as wearing a long-sleeved shirt, rubber gloves or mask, was not associated with leptospirosis seropositivity among the respondents in this study. This finding was similar to that of a study conducted among town service workers in northeastern Malaysia in 2008 (Sulong et al., 2011). Another study among abattoir workers in New Zealand also reported that wearing PPE (e.g., gloves, a facemask, safety/ normal glasses or a balaclava) was not protective against leptospiral infection (Dreyfus et al., 2015). In Thailand, it was also reported that the use of gloves and long-sleeved shirts was not associated with leptospirosis (Phraisuwan et al., 2002), while a population-based case-control study in Brazil revealed that the use of gloves while working was not a protective factor against leptospirosis (Sarkar et al., 2002).

Proper handwashing is an important preventive measure against leptospiral infection because it removes potentially contaminated water or soil from the hands. This is also consistent with the fact that the transmission of leptospirosis may occur through ingestion (WHO, 2003). In the present study, this factor was found to be protective against leptospiral infection, and this finding aligns with the results of a 2008 study among town service workers (Sulong et al., 2011). A cohort study conducted in Sweden with employees engaged in post-flood management activities reported an association between neglecting handwashing after contact with floodwater/sediment and the risk of illness (Wojcik et al., 2013). However, this factor was not found to be significant in a study of 150 workers in a slaughterhouse in Brazil (Gonçalves et al., 2006).

Contact with secretions, blood or urine of animals while working, especially leptospire-infected reservoirs, might predispose workers to leptospirosis via a direct transmission (Bharti et al., 2003). In the present study, workers who had contact with animals while working had two times the odds of having

leptospirosis compared to those who had no contact with animals while working (Adj. OR: 2.09; 95% CI: 1.06, 4.11; p = 0.033). Those with reported animal contact stated rodents, cows, sheep and rabbits as examples of the common animals they had contact with while working. One respondent also stated that he had contact with a dog while working. These animals are known reservoirs for leptospires, and other studies have found that the odds of developing leptospirosis increase when there is contact with these animals. A study conducted in western Jamaica discovered that contact with rodents and goats increased the odds of leptospirosis by about four and three times, respectively (Keenan et al., 2010). Increased risk due to animal contact was also seen in studies in Iran (Alavi et al., 2014). In contrast, no association was found in some studies conducted in Malaysia (Sulong et al., 2011) and Brazil (Lacerda et al., 2008).

Rodents are important reservoir hosts for pathogenic serovars of *Leptospira* and are the most common source of human leptospirosis (Bharti et al., 2003). In the present study, a significant association was found between the sighting of rats or other rodents in the workplace and seropositivity for leptospirosis among town service workers. Those who had seen rats or other rodents at their worksite had two times the odds of being seropositive for leptospirosis compared to those who had not seen rats or rodents at their workplace (Adj. OR: 2.17; 95% CI: 1.11, 4.25; p = 0.024). This might be due to the workers being in contact with rats; some were involved in pest control in areas with high rodent populations. A cross-sectional study among butchers and their assistants in Jamaica also found that sighting live rodents in the slaughterhouse played a significant role in leptospirosis seropositivity among the respondents (Brown et al., 2011). This finding is in agreement with the results of a study conducted in Salvador, Brazil (Sarkar et al., 2002). Nonetheless, studies among high-risk occupational groups found no association between the sighting of rats or other rodents at the workplace and leptospirosis seropositivity (Sulong et al., 2011).

When environmental factors were taken into account, the present study revealed that residing near a river (within 200 m) was a significant factor associated with leptospirosis. Workers who resided ≤200 m from a river had about two times the odds of being seropositive for leptospirosis compared to those who resided more than 200 m from a river (Adj. OR: 1.84; 95% CI: 1.03, 3.28; p = 0.039). Similar findings were reported in studies conducted in India (Philip et al., 2013) and in a previous study on leptospirosis among town service workers in Malaysia (Sulong et al., 2011). These findings suggest that the respondents were at higher odds of exposure to *Leptospira* if they were engaged in water-related activities or experienced flood-related problems near their houses. However, the finding contradicts other studies conducted around the world that reported no association between the distance of a house from a river and leptospirosis (Nardone et al., 2004).

Among the limitations of the present study is the fact that the job category was not considered an occupational factor. The number of respondents in the garbage collector job category was too small to permit a comprehensive assessment of the probable risk factor. Despite our effort to explain the importance and confidentiality of the study to the respondents during data collection and the support of the supervisors and heads of departments, it was noted that workers, especially from the garbage collector job category, refused to take part in the study due to personal reasons. As participation was voluntary and considering the need to comply with the ethical guidelines, we respected their decision not to join the study. A similar problem of small sample size in a certain job category also occurred in another study among town service workers; in that case, the researchers also did not analyse the association between the job category of the respondents and leptospirosis seropositivity (Sulong et al., 2011).

CONCLUSION

Several demographic, occupational and environmental factors were found to be significantly associated with leptospirosis seropositivity among town service workers in northeastern Malaysia. In terms of occupational risk factors, those who did overtime work, had animal contact while working, sighted rats at the worksite and lived ≤200 m from a river were at high risk of leptospirosis infection. Thus, prevention and control strategies for leptospirosis will need to focus on possible sources of leptospirosis transmission and high-risk activities in the workplace.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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CASE REPORT

Management of Bilateral Extensive Subcutaneous Emphysema

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ABSTRACT

Subcutaneous emphysema (SE) occurs when there is a trapping of air under the skin due to leakage either from the gastrointestinal or respiratory tract. SE is commonly associated with procedural complications such as chest tube insertion, cardiothoracic surgery; as well as barotrauma, infection and malignancy. The majority of SE resolve spontaneously without any active intervention. However, it is a medical emergency as SE may spread and compromise the airway. Various interventions had been described in other literature. We would like to illustrate a case of extensive SE one day after chest tube insertion for secondary spontaneous pneumothorax, successfully relieved by usage of cannulas and low-grade pressure suction.

INTRODUCTION

Subcutaneous emphysema (SE) occurs when air passes through ruptured alveolus to pulmonary interstitial tissue. As the pressure is greater than pleural reabsorption, it causes air to be trapped under the skin. SE is commonly associated with chest drain insertion or cardiothoracic procedures, and self-limiting. Palpable crepitation over the skin with widespread soft tissue distention is a typical clinical sign of SE. Rarely, SE can progress further and involves a larger area of the chest, leading to cardio-respiratory arrest if no preventive measures are taken to address this issue (William et al., 2005). Several methods of managing extensive SE had been reported such as emergency tracheostomy,

multisite subcutaneous drainage, suction pressure from a chest drain, etc. We would like to report a case of extensive SE developed one day after chest tube insertion for secondary spontaneous pneumothorax and our methods to relieve the SE.

CASE PRESENTATION

A 52-year-old gentleman with underlying chronic obstructive pulmonary disease (COPD), presented with dyspnoea and productive cough for two days. He denied fever, chest pain and hemoptysis. He was tachypneic with an oxygen saturation of 88% upon arrival. His arterial blood gas showed hypoxia with partially compensated respiratory acidosis. An urgent chest radiograph was performed which showed right pneumothorax (3cm size of pneumothorax from right hilar) (Figure 1A). A chest drain (24-French) was inserted immediately at the right fifth intercostal space at the safety triangle. He was much relieved after chest drain insertion (Figure 1B).

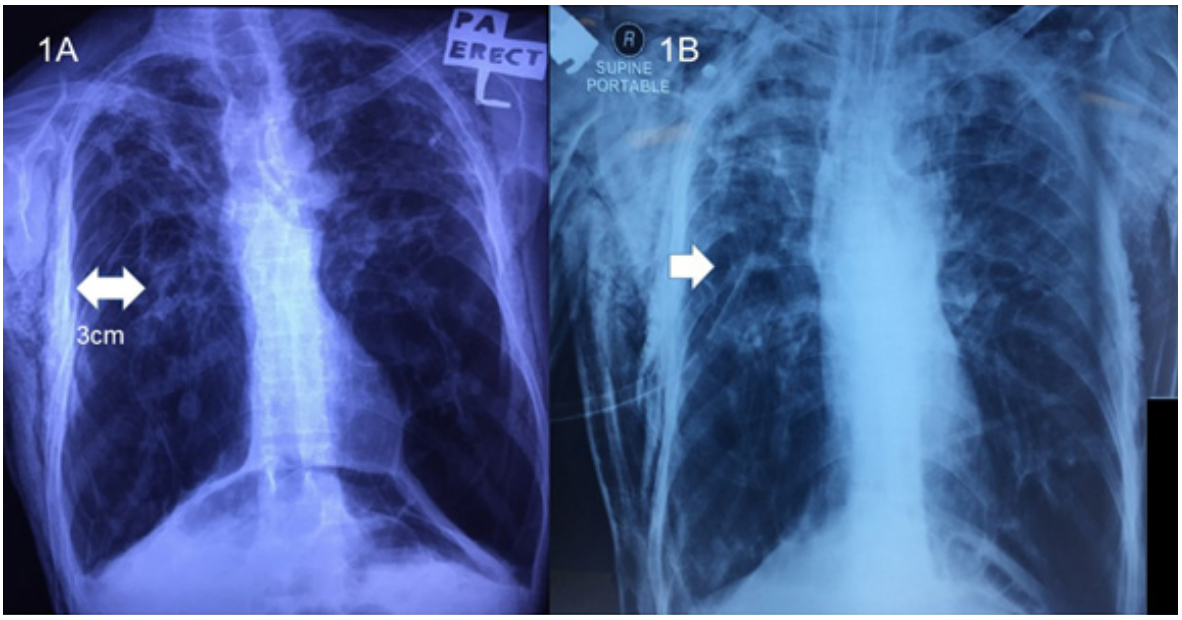

Figure 1A Chest radiograph (on admission) showed right pneumothorax with size 3 cm from hilar with bilateral bronchiectasis changes**. Figure 1B** A 24 French size chest drain was inserted (white arrow showed the tip of the chest tube) and the right lung was successfully re-expanded. There was also subcutaneous emphysema seen over the right chest wall (A chest radiograph was taken after the patient was intubated due to respiratory distress).

The next day, the patient developed SE over his bilateral anterior chest wall which gradually extended over to his neck, cheek, bilateral arms, torso and thighs. He was unable to open both of his eyes due to the extensive SE (Figure 2A). At the same time, his underwater seal draining was noted to have an increasing amount of bubbling (air escape). Subsequently, he developed acute respiratory distress with dysphonia. To protect his airway, he was electively intubated and received mechanical ventilation. Chest radiograph performed later showed re-expansion of the right lung with extensive SE seen over the chest wall (Figure 1B). An urgent computed tomography (CT) of the thorax showed extensive SE. There were also emphysematous lung changes with bilateral apical bronchiectasis in keeping with chronic lung disease complicated with right pneumothorax (Figure 3A & 3B). Large bullae were seen at the apical segment of the right upper lobe measuring 3.1 cm × 3.6 cm × 2.3 cm. As such, he developed extensive subcutaneous emphysema with broncho-pleural fistula formation due to chest drain insertion.

Figure 2 The appearance of the patient before (Figure 2A) showed extensive SE involving bilateral anterior chest wall, upper limbs, cheek and neck and 10 days later (Figure 2B) showed resolve SE.

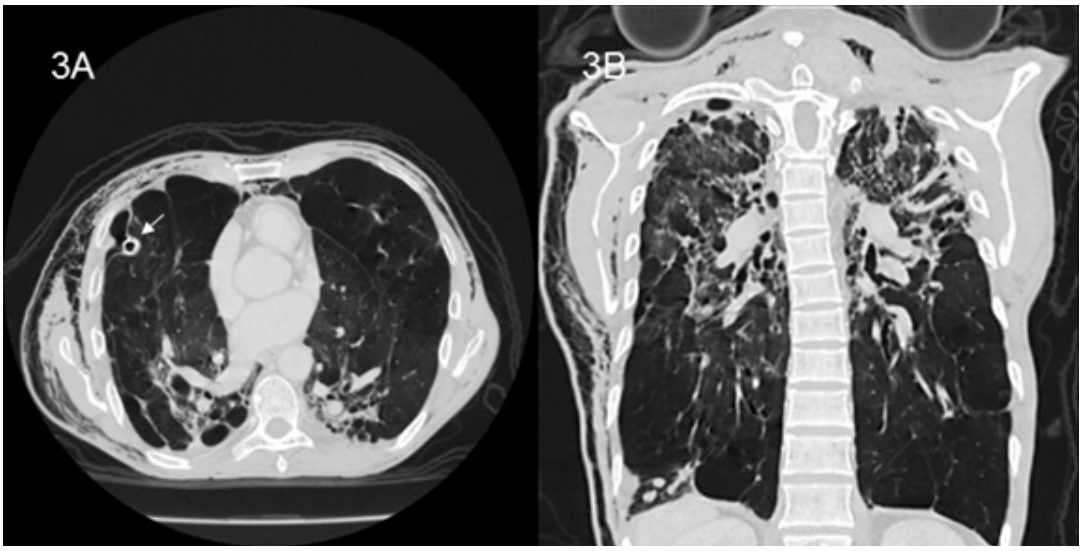

Figure 3A (Axial view) and **Figure 3B** (Coronal view) CT thorax showed extensive SE. Emphysematous lung changes with bilateral apical traction bronchiectasis in keeping with chronic lung disease complicated with right pneumothorax. (Arrow showed the chest tube location).

Two 16-Gauge size cannulas were inserted subcutaneously on his anterior chest wall with a low-grade suction of -5cmH_2O applied over his right chest drain as well. Active compressive massage over the face and chest wall area towards the cannula site every 2 hourly during the first 24 hours was performed to facilitate the drainage of the trapped air in the subcutaneous tissue. The SE resolved gradually and he was able to open both of his eyes. His oxygen supplementation was reduced gradually and he was successfully extubated 3 days later. The low-grade pressure suction over the right chest drain was continued for a week. His subcutaneous emphysema resolved completely without any adjustment of the chest tube and eventually, we were able to remove his chest drain (Figure 2B).

DISCUSSION

The main aim of managing extensive SE is to decompress the thoracic outlet and the neck to ensure airway patency. Massive SE can become a life-threatening event if the airway and cardiovascular are compromised (William et al., 2005). In this case, our patient developed an extensive SE secondary to broncho-pleural fistula after chest drain insertion. We inserted two 16-Gauge size cannulas subcutaneously at his anterior chest wall and a low-grade pressure suction of −5cm H_2O was applied over his right chest drain.

According to Srinivas et al. (2007), the most crucial step in managing SE effectively by using microcatheter drainage is to increase the interstitial hydrostatic pressure by applying compression massage from the face downwards and arm upwards directions respectively towards the catheter site. The resolution of extensive SE only happens after the steps mentioned above were performed (Srinivas et al., 2007). Paul et al. (2002) reported success in managing a patient with recurrent pneumothorax and persistent air leak complicated with extensive SE by using two 14-gauge angiocatheters which were inserted into the subcutaneous space bilaterally at the second intercostal space, midclavicular line. Angiocatheters were modified to create multiple fenestrations on them. By applying this method, SE and pneumothorax were resolved within three days (Paul et al., 2002). Another case reported by Brenton (2018) described the usage of three 14-gauge angiocatheters inserted subcutaneously in different directions and positions over the chest wall in a case of post esophagogastrectomy patient who developed extensive SE. The SE completely resolved within 24 hours after the angiocatheters were inserted (Brenton, 2018).

There are other methods of managing SE which have been reported in the literature. Most of the methods were more invasive and could potentially cause more discomfort to the patients. One of the methods is making a horizontal incision over bilateral clavicles into the fascia region, which is reported by Matthew and Colin (2013) in a perforated duodenal ulcer patient who developed massive SE. Other methods of managing extensive SE such as inserting a trochar-type chest drain subcutaneously from the mid-axillary line and tunnelling it towards the jugular notch (Terada, 1993), insertion of Jackson-Pratt drain over bilateral anterior mid-chest wall (Sherif et al., 1999) and emergency tracheostomy (Lopez et al., 1997).

CONCLUSION

In summary, we described the usage of two wide-bore cannulas with low-grade suction from chest drain in managing extensive SE. The tools needed are relatively cheap and accessible in most of the general medical wards. Moreover, the procedures can be done bedside by physicians. This treatment aims to relieve the discomfort and avoid complications arising from SE while providing a simple, yet cost-effective as well as the low-risk approach in decompressing SE.

CONFLICT OF INTEREST

The authors declare that they have no competing interests in publishing this case.

CONSENT

The authors certify that written consent was obtained from the patient to publish this case report. The patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that his name and initials will not be published, and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed. A copy of the written consent is available for review by the Chief Editor.

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CASE REPORT

Neurofeedback (NFB) Training in Aspergers

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ABSTRACT

The prevalence of Autism Spectrum Disorder (ASD) is increasing globally. Due to its high incidence rate reported globally, ASD should be considered as a public health emergency that requires immediate attention to the process of screening, diagnosis, and intervention. This is a preliminary case study to test the efficacy of the neurofeedback technique in helping an Asperger's child to reduce his pathological symptoms (e.g., sociability, sensory/cognitive awareness, communication/ speech/ language, and physical behaviour). Neurofeedback is brain training based on the operant conditioning concept to regulate brainwave activities voluntarily using audio or visual feedback (real-time). In this study, we conducted neurofeedback training on an eight-year-old boy diagnosed with Aspergers aimed to enhance Sensorimotor Rhythm (SMR) wave (12 to 15 Hz) and at the same time inhibiting theta wave (4-8 Hz) and high beta wave (22-36Hz) at C4 over the right motor area, with the reference electrode placed on A2 and ground electrode placed on A1. Twenty (20) sessions of neurofeedback training were conducted on the boy's aims to improve his behaviour and emotional expression, language comprehension. The participant showed observable improvement after 20 sessions of neurofeedback training in sociability and speech/ language or communication subscale of the Autism Treatment Evaluation Checklist (ATEC), and parent's report. This study provided important evidence that neurofeedback training can be employed to improve the child's Asperger's symptoms.

INTRODUCTION

Years ago, autism was a rare diagnosis but now it has been seen the rise of a seeming epidemic. Autism and Asperger's is a spectrum of pervasive developmental disorders that can disrupt a person's ability to communicate with other people and to interact with the outside world. It is defined as an impairment in communication and restricted, social interaction, repetitive, and stereotyped patterns of behavioural interests that limit learning, interpersonal, and occupational functioning (Chapin & Russell-Chapin, 2014). The child seems normal infants and toddlers, normally by age three. The effects of this spectrum on the child's lives are stricken and its effects on their families can be ranged from difficult and sad to heartbreaking and catastrophic.

The Centre for Disease Control reported a rising percentage of the world population diagnosed with an autism spectrum disorder (ASD). According to the statistic in 2014, an estimated one (1) per cent of the world population had been diagnosed an ASD, an estimated 3.5 million population of the United States, or one (1) in 68 American children living with ASD. In 2013, the National Autism Society of Malaysia (NASOM) reported in the past three years there was a 30% increase in the intake of individuals with autism in the organization. Statistics in the year 2018 estimated 300,000 people living with ASD in Malaysia (New Strait Times, 2018).

There are many types of interventions that have been implemented to help autistic children, however, there were no definitive treatments or cures for this disorder. There are also no specific therapeutic guidelines that can be referred to reduce the disorder symptoms, increase life functioning, and thus improve the quality of life of people with autism. Conventional medicine considers autism as a psychosocial disorder, and strongly reliant on inherited genes. This disorder was not thought to be curable, thus the approved treatments normally included drugs and the therapies program designed to improve life functioning, such as behaviour modification and/or speech therapy (Hill & Castro, 2009). The Autism Research Institute lists treatments, including drugs, nutritional supplementation, hyperbaric oxygen treatment, allergy treatment, removal of heavy metals (chelation), and dietary changes.

Neuroimaging therapies have demonstrated that autism is a neurological disorder that reveals distinct abnormalities in the brain. Neuropsychologist Rob Coben has studied the brainwave activity of autistic children extensively. His research findings revealed that the brains of children with autism have areas that are too loosely connected (Coben & Padolsky, 2007). Too many leads to decreased resilience and reduced ability to reorganize itself, and too little decreases the communication necessary to organize by reducing the numbers and intricacies of the interfaces.

Neurofeedback is the method developed in neurophysiological labs of scientific institutes in the USA and has been proven to be effective in altering brain activity. It is a computerized method based on tracking the electrical activity of the brain (EEG) and giving feedback about the brain activity to the therapist, however, the extent to which such alterations can influence behaviour is still unknown. Vernon (2003) claimed that previous studies have indicated that neurofeedback can be used to help treat a number of some early childhood disorders as such attention-deficit/hyperactive disorder (ADHD), Aspergers's disorder, learning disability, obsessive-compulsive disorder (OCD), and ASD (Demos, 2005; Evans, 2002). Several randomized clinical studies on the usage of neurofeedback techniques have proven the efficacy of neurofeedback technique for ADHD (Bakhshayeshet al., 2011; Gevensleben et al., 2010; Liechti et al., 2012). The findings have led to studies of neurofeedback as an alternative

treatment for autism since generally autistic children show symptoms of attention deficit and hyperactivity (Wang et al., 2013). This preliminary case study aimed to test the efficacy of neurofeedback training in helping an Asperger's child to reduce his pathological symptoms (e.g., sociability, communication/ speech/language, sensory/cognitive awareness, and physical behaviour).

CASE PRESENTATION

An eight-year-old boy is not attending formal school programmes. The school that he attended to enter rejected him due to his agitation behaviours, difficulties in focusing and social relations with other children, and not speaking well. He was accompanied by his mother who came for the training at the university Bio-Neurofeedback Lab in March 2019. He was diagnosed with Asperger's syndrome when he is in three-year-old. He had received various therapies and programmes before coming for neurofeedback training.

Neurofeedback Training (NFT)

The boy has attended NFT since March 2019 and had completed approximately 15 hours of NFT (20 sessions of NFT). He was accompanied by his mother to the Bio-Neurofeedback Lab average twice a week and completed a session that lasted 30 to 45 minutes. During each NFT session, a protocol consisted of a three-minute baseline set, followed by 10 three-minute intervals of neurofeedback training (e.g., video game). Neurofeedback intervals were separated by short rest periods every three-minute video game. The video game included: Mazes, Variable-Dot-Mazes, Island, Highway, and Jump box. He had the choice of the video games he wanted to play at each session. The computer system used for NFT was EEGer Neurofeedback System Device and the operating system was using a personal laptop and television monitor.

Before the NFT, the mother was interviewed to examine the anamneses of him, his family history, and his current problems. Procedures and possible side effects of the NFT were explained to the mother and the informed consent was signed by the mother. Then, pre-baseline performance tests consisting of a symptom checklist, Autism Treatment Evaluation Checklist (ATEC), The Autism Rating Scale (CARS), and Quantitative EEG (qEEG) were conducted. The Autism Treatment Evaluation Checklist (ATEC), The Autism Rating Scale (CARS) were repeated after 20 sessions and compared with his pre-baseline performance results to estimate behavioural improvements. Symptom profiles were reviewed at each session.

For administered protocols, the 20 sessions of the NFT were aimed to enhance SMR wave (12 to 15 Hz) and at the same time inhibit theta wave (4 – 8 Hz) and high beta wave (22 – 36 Hz) at C4 over the right motor area, with the reference electrode placed on A2 and ground electrode placed on A1. Many trainers such as Margeret Ayers, Othmers, and Lubar (Soutar & Longo, 2011) prefer to begin at the motor strip area. Othmers (2008) stated that the largest and oldest pyramidal cells are in the motor strips area, so it is easiest to influence thalamic oscillators from this area. This protocol was recommended to improve autistic behaviour.

Autism Treatment Evaluation Checklist (ATEC)

Autism Treatment Evaluation Checklist (ATEC) was developed by Rimland and Edelson (1999). The ATEC is designed specifically to measure the effectiveness of various treatments. It is not a diagnosis checklist but a checklist that provides a general condition of a child's current behaviours and skills. The ATEC consists of four subtests: (a) Speech/Language Communication (14 items: Scores range from 0 to 28); (b) Sociability (20 items: Scores range from 0 to 40); (c) Sensory/ Cognitive Awareness

(18 items: Scores range from 0 to 36); and d) Health/ Physical/ Behaviour (25 items: Scores range from 0 to 75). The four subscale scores can be used to calculate a total score (total scores can range from 0 to 180). The lower the score, the less impaired the participant. The age range for the ATEC is 2 years of age and older. The parents, teachers, or caretakers were asked to complete the instrument. ATEC provides a total score and subscale scores. The higher the score, the more serious the problems or reverse. The total score and scores of each subscale can be extrapolated to determine the percentile of the severity of the participant in comparison with score distributions provided by the Autism Research Institute (Table 1).

Table 1 The percentile of the severity of the Autism Treatment Evaluation Checklist (ATEC)

	Scale I	Scale II	Scale III	Scale IV	
	Speech	**Sociability**	**Sensory/ Cognitive**	**Health/ Physical/ Behaviour**	**Total Range: 0 – 180**
	Range: 0 – 28	Range: 0 – 40	Range: 0 – 36	Range: 0 – 75	
Centile					
Mild	0 – 2	0 – 4	0 – 5	0 – 8	0 – 30
0 – 9	3 – 5	5 – 7	6 – 8	9 – 12	31 – 41
10 – 19	6 – 7	8 – 10	9 – 11	13 – 15	42 – 50
20 – 29	8 – 10	11	12 – 13	16 – 18	51 – 57
30 – 39	11 – 12	12 – 13	14 – 15	19 – 21	58 – 64
40 – 49	13 – 15	14 – 15	16 – 17	22 – 24	65 – 71
50 – 59	16 – 19	16 – 18	18 – 19	25 – 28	72 – 79
60 – 69	20 – 21	19 – 21	20 – 21	29 – 32	80 – 89
70 – 79	22 – 24	22 – 25	22 – 25	33 – 39	90 – 103
80 – 89	25 – 28	26 – 40	26 – 36	40 – 75	104 – 179
90 – 99					
Severe					

Source: Autism Research Institute (retrieved from https://www.autism.org/autism-treatment-evaluation-checklist/interpreting-atec-scores/ on 8 November 2019)

Symptom Checklist

The symptom checklist used in this study was designed by the New Mind Neurofeedback Center (Soutar & Longo, 2011). The checklist was used at the beginning of each neurofeedback training session. The checklist was used to help evaluate and track the participant's neurofeedback training progress. The checklist consisted of 16 items (e.g., short-term memory, concentration, motivation/ energy, assertiveness, restlessness, negative mood, negative emotions, quality of sleep, positive moods, appetite, worry/ negative thinking, patience, pain/ physical discomfort, fatigue, and irritability) that rate on a scale of 1 to 10, 1 is rated as low, little, or poor, and 10 is rated as high, a lot, or excellent. Impulsivity that is measured in this checklist includes disorganization, foot in mouth, impulse buying, blowing up at people, and so forth. And the distinction between emotion and mood is an emotion lasts 20 minutes to an hour, however, a mood lasts several hours, days, or weeks.

Autism Treatment Evaluation Checklist (ATEC) Results

This boy has attended NFT for about five months. After 20 NFT sessions improvement was detected in all four subtests of ATEC. Especially, for Speech/ Language/ Communication improved 80%, from score 20 (centile of 20 – 29) to score 2 (mild) and Sensory/Cognitive Awareness improved 88%,

from score 18 (centile of 50 – 59) to score 2 (mild). Sociability improved only 9%, from score 22 (centile of 70 – 79) to score 20 (centile of 60 – 69); and Health/ Physical Behaviour improved 19%, from score 41 (centile of 80 – 89) to score 33 (centile of 70 – 79); and from a total score of 91 (centile of 70 – 79) improved to score 57 (centile of 20 – 29) (37%). Table 2 showed the distinction between the baseline ATEC scores and the client's ATEC scores after neurofeedback training.

Table 2 Autism Treatment Evaluation Checklist (ATEC) results for the boy before and after Neurofeedback Training

NFT	Autism Spectrum Level				
	Speech/ Language/ Communication	Sociability	Sensory/ Cognitive Awareness	Health/ Physical Behaviour	Total
Before NFT	10 (centile of 20 – 29)	22 (centile of 70 – 79)	18 (centile of 50 – 59)	41 (centile of 80 – 89)	91 (centile of 70 – 79)
After NFT	2 (Mild)	20 (centile of 60 – 69)	2 (Mild)	33 (centile of 70 – 79)	57 (centile of 20 – 29)
Improvement	8	2	16	8	34
Percentage of Improvement	80%	9%	88%	19%	37%

Behaviour Symptom Checklist Results

After 20 NFT session, results also indicated a substantial decline in his autistic behavior especially, in restlessness (improved 32.56%); irritability (improved 30.23%); impulsivity (improved 30.0%); worry/negative thinking (20.51%); negative mood (improved 17.50%) and negative emotions (improved 13.16%) (Table 3).

Parent's Report

In the interview conducted with the mother related to her observation of her son throughout the 20 sessions of neurofeedback training, the mother reported that he has shown marked symptom decrease. He was more awake, more concerned, and more interested in his surroundings after neurofeedback training. His mother was also reported that he used more complicated and logical speech, spoke more clearly and understandably. Besides, the mother reported considerable improvements in his social interaction, reduction in temper tantrums, and better control of emotion and mood changes. Some examples of the mother responses based on her observation of her son were *"… this morning he (her son) asked me whether I have taken my breakfast. This is the first time he asked me and never happen before …."*, *"… I cut my finger yesterday, I brought him with me to the medical hospital he just sits quietly while we were waiting for the doctor. He seems like worry about me …."*, *"… he fought with a friend in the tuition class yesterday. Fighting for a toy and the toy was belong to his friend. When I asked him to return the toy to his friend, he got angry and* temper tantrums. *But he can calm down fast than before…"*, and *"… he quarrelled with his sister yesterday. His sister was so angry with him. He scarred the sister does want to make friends with him so he wrote an apology letter to her sister…."*

Table 3 Behaviour Symptom Checklist Results of the boy before and after Neurofeedback Training

Session	Concentration	Short-term memory	Quality of sleep	Appetite	Motivation/Energy	Domestic Violence	Delusion	Anxiety/Panic	Restlessness	Worry/Negative thinking	Negative Mood	Negative emotion	Pain/Physical Discomfort	Fatigue	Irritability	Impulsivity
The average first 5 Sessions	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
The average Final 5 Sessions	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Average % Improvement (%)	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
(Improvement)	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Brain Wave Pattern

After completing 20 sessions of NFT at C4, the result of the boy's brain wave pattern as shown in Figures 1 and 2. The result revealed a reduction of the ratio of theta/beta wave, SMR power (12 – 15 Hz) increased over time at C4. However, theta and high beta power were not stable over the 20 sessions.

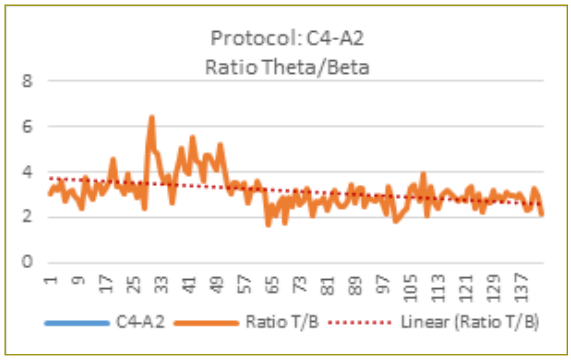

Figure 1 The ratio of theta/ beta wave

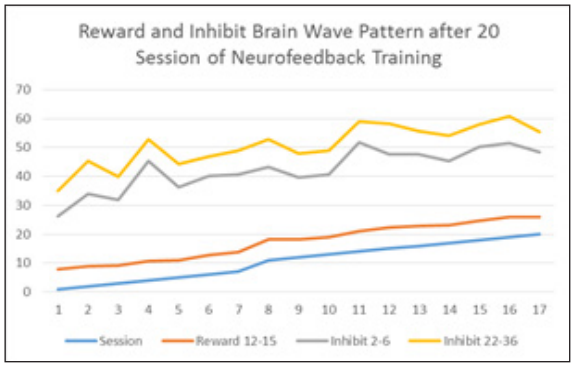

Figure 2 SMR, theta, and hi beta brain

Neurofeedback is believed can change and elicit growth at cellular levels of the brain, which in turn will improve behavioral cognitive performance and brain functioning (Demos, 2005). Neurofeedback training has been proved to be useful in the treatment of different disorders in adults and children. The finding in this case study presented another evidence of the efficacy of neurofeedback training for individuals with Asperger's Syndrome. After 20 sessions of NFT at C4 that aimed at rewarding SMR (12 – 15 Hz), inhibiting theta (4 – 8 Hz), and inhibiting high beta (22 – 36 Hz), results revealed a significant decline in his autistic behaviour as reflected in the Autism Treatment Evaluation Checklist (ATEC). Especially, in Communication/Speech/ Language and Sensory/Cognitive Awareness. The moderate improvement was also detected in the total score of the measure and Health/ Physical behaviour component and only a small improvement was detected in the child's Sociability component. The improvement in his behaviour also was reported by the mother in the behaviour symptom checklist which revealed a substantial decline in his restlessness, irritability, impulsivity, worry/ negative thinking, negative mood, and negative emotions. Parent reports furthermore indicated considerable improvements in his communication, social interaction, reduction on temper tantrums, better control on emotion and mood changes, more awake, concerned, and interest in surroundings. Furthermore, the boy's brain wave patterns were also changed in a more positive direction after 20 neurofeedback training sessions at C4.

DISCUSSION

The findings of the current study are consistent with the neurofeedback study conducted by Scolnik (2005) with five (5) children diagnosed

with Asperger disorder, the study also indicated that after 24 sessions of neurofeedback training aimed to reward 12 – 15 Hz lower beta range and to inhibit 4 – 10 Hz theta band, the parents and teachers reported improvements in the participants' behaviour, such as higher self-esteem, more empathy, less anxiety, more flexibility, increased social interaction, improvement in fewer severe mood changes and frustration toleration.

The finding also showed that the theta/ beta ratios changed in a positive direction for their two participants. Sichel et al. (1995) in their neurofeedback study of an 8-year-old boy with attention impairments and a mild form of autism, reported that after 31 neurofeedback sessions aimed to inhibit theta (4 – 8 Hz) and rewarded low beta (12 – 15 Hz), the boy showed positive changed in all the diagnostic criteria of autism in DSM-III-R (e.g. more attending, more talking, more eye contact with others, more imaginative play and seeking comfort).

The results of the current study have further supported the study by Jarusiewicz (2002) for a relation between theta/beta power and autism. Jarusiewicz (2002) investigated the influence of neurofeedback training in 12 autistic children aimed to inhibit theta (2 – 7 Hz) and reward SMR activity (10 – 13 Hz) over the right motor area. Jarusiewicz (2002) reported a significant decline in autistic behaviour for the 12 autistic children as compared to the control group. Parent reports indicated improvements in socialization, anxiety, vocalization, tantrums, sleep, and schoolwork. Whereas, no or minimal changes were found for the control group. The findings of the current study and previous studies (Jarusiewicz, 2002; Scolnik, 2005; Sichel et al., 1995) suggested that neurofeedback protocols that inhibit theta and reward low beta or SMR may hold particular value for the treatment of autistic children. The findings of the current study also provide further evidence in supporting the efficacy of neurofeedback training in helping an Asperger's child to reduce pathological symptoms (e.g., speech/ language/ communication, sociability, sensory/ cognitive awareness, and physical behaviour). Importantly, these findings provide important information that through which we can understand the relation between SMR, theta power, and autistic pathological symptoms.

CONCLUSION

In conclusion, the finding in this case study presented another evidence of the efficacy of neurofeedback training for Asperger's Syndrome. The current study suggested that neurofeedback protocols that inhibit theta, high beta, and reward SMR showed particular value for the treatment of autistic children. Although the current findings are encouraging, the limitation of the case study method and the influence of situational variables (e.g., daily activities of the child, therapies attended, diet, surrounding environment, etc.) need to take into consideration. Thus, further methodological improvement is necessary for the form of sample sizes, a more accurate description of sample characteristics, controlled studies, and follow-up studies.

CONFLICT OF INTEREST

The authors declare that they have no competing interests in publishing this case.

CONSENTS

Written consent was obtained from the patient's mother to publish this case report. A copy of the written consent is available for review by the Chief Editor.

ACKNOWLEDGEMENTS

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CASE REPORT

Partial Cyst Resection, Fabrication, Imbrication and Duraplasty of Symptomatic Sacral Tarlov Cysts

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ABSTRACT

Tarlov cysts are pathological cerebrospinal fluid-filled sacs located in the space between the perineum and endoneurium of the nerve roots. Symptomatic Tarlov cysts are extremely rare. There is no consensus regarding the optimal surgical treatment for it up to date. We encountered a recurrent symptomatic sacral Tarlov cyst of a patient whose symptoms resolved after undergoing partial cyst resection, fabrication, imbrication, and duraplasty of sacral Tarlov cysts. A 53-year-old man was initially presented with worsening lower back and buttock region pain, sensory changes involving S1 – S3 distribution of the left lower limb in 2014. The initial magnetic resonance imaging (MRI) lumbosacral had been carried out and revealed a perineural cyst at the level of S1 – S3. The patient did S1 – S3 laminectomy, fabrication, and imbrication after failed conservative treatment and his symptoms resolved for three years. However, similar symptoms recurred in 2017 and the repeated MRI revealed a recurrent well-defined multiloculated cystic structure was seen arising from the spinal canal of S1 – S3 level. The second time, the patient underwent laminectomy S1 – S3, partial cyst resection, fabrication, imbrication, and duraplasty of the sacral region. Many proposed surgical options are available for treating the symptomatic Tarlov cysts. There is no literature reviewed on the best surgical option for the recurrent symptomatic Tarlov cyst. We proposed sacral laminectomy, partial cyst resection, imbrication, fat graft packing, fabrication, and duraplasty in recurrent symptomatic sacral Tarlov cyst.

INTRODUCTION

Tarlov cysts are also known as perineural cysts (Tarlov, 1970), are pathological cerebrospinal fluid-filled sacs situated in the space between the perineurium and endoneurium of the nerve roots (Goyal et al., 1987). It has been estimated that around 1.5% of people have more than one Tarlov cyst, with about 13% of them being symptomatic (Langdown et al., 2005). They are commonly found near the junction of posterior and dorsal root ganglion, and they are bordered by the nerve of reticular fibres. Tarlov cysts are commonly found in the sacral region. Individuals may be affected by multiple cysts of various sizes. The cause of Tarlov cysts is still unknown, it may be either congenital or acquired. Tarlov proposed that these cysts could form due to an increase in cerebrospinal fluid hydrostatic pressure, where the pressure is exerted by the fluid due to the force of gravity (Tarlov, 1970).

The larger the cyst is, the more likely it is to cause symptoms. Although they are asymptomatic typically, 1% may grow and contribute to symptoms include chronic pain at the lower back, especially below the waist, spreading to the buttocks and legs, paresthesias, bowel, and urinary incontinence, impotence, and rarely, weakness in the legs (Tani et al., 2013).

Computed tomography (CT) myelography and lumbosacral MRI are the most common investigations of diagnosing Tarlov cysts. However, dedicated sacral MRI has proven to be more sensitive (Murphy et al., 2016).

Many treatment options are available for symptomatic Tarlov cyst treatment that was being described in the literature ranging from non-surgical, minimally invasive procedures (lumbar cerebrospinal fluid drainage and CT guided aspiration of the cyst) and surgical procedures (such as fenestration of cyst, shrinkage of the cyst by using cauterization technique, marsupialization, partial excision and oversewing of the cyst wall, and total excision of the cyst together with nerve root) (Medani et al., 2019).

Surgical techniques such as lumbo-peritoneal shunting, shunting of cyst to subarachnoid, and decompressive laminectomy were uncommonly being practiced[7], herein, we report a case of recurrent sacral Tarlov cyst compressing the S1 – S3 perineural sheath and eventually requiring S1 – S3 laminectomy, partial resection of Tarlov cyst, nerve root imbrication, fat grafting packing, followed by fabrication and duraplasty.

CASE PRESENTATION

A 53-year-old man with no significant medical illness and family history came to IIUM@ SASMEC neurosurgical department in 2014, initially presented with worsening lower back and left buttock region pain with left-sided S1 mapping radicular pain which worsened upon prolonged standing and sitting position, paresthesia in S1 to S3 distribution of the bilateral lower limb without motor weakness over the left lower limb. The patient also had no urinary or bowel incontinence. The initial MRI lumbosacral had been carried out and revealed a perineural cyst at the level of S1 – S3. The patient did S1 – S3 laminectomy, fabrication, and imbrication after failing a conservative treatment trial for 6 months (oral pregabalin and physiotherapy) and his symptoms resolved for three years.

He started to have similar symptoms as described in the initial presentation and required occasional usage of analgesics in 2017. However, his symptoms became worse and warranted for another MRI to reassess the lesion. His MRI revealed a recurrent well-defined multiloculated cystic structure that follows cerebrospinal fluid signal intensity in all sequences (hypointense on T1, hyperintense on T2) (Figures 1 and 2) was seen arising from the spinal canal of S1 – S3 level, measuring about 1.9 × 3.0 × 4.3cm. Thin internal septations were seen within. The sacral exiting nerve roots were displaced laterally bilaterally.

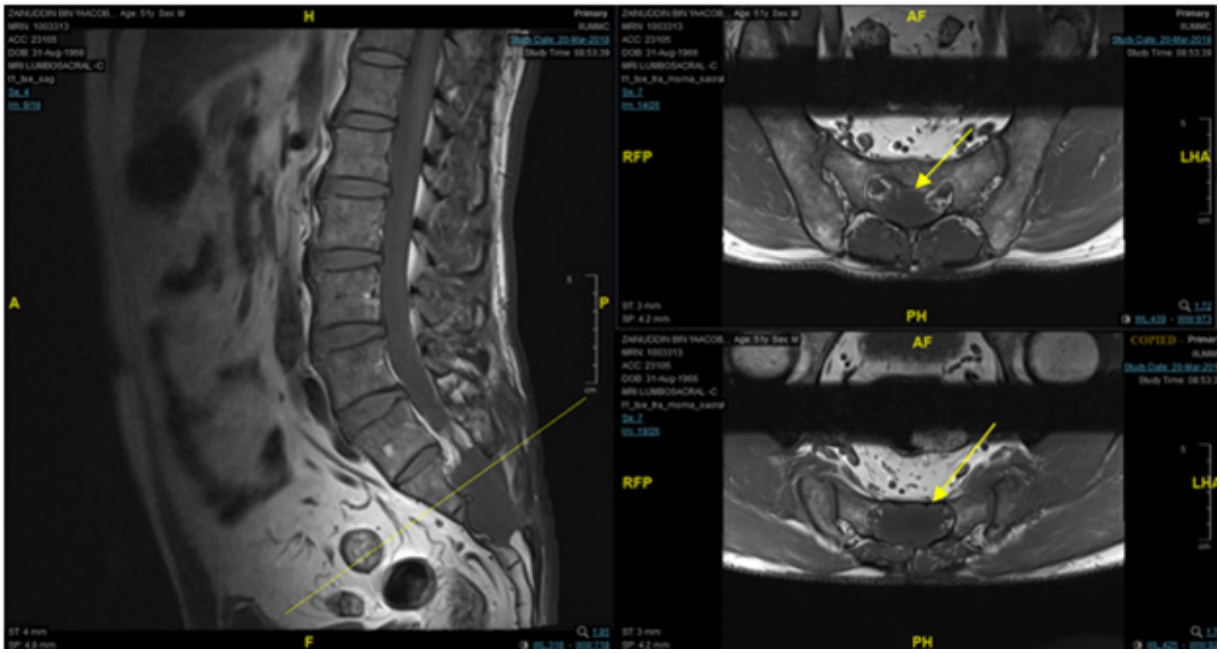

Figure 1 T1-weighted lumbosacral MRI images. Sagittal (a), axial (b, c) views show the well-defined cystic structure (yellow arrow) at the S1 vertebra (b) and the S2 vertebra (c). Preoperative magnetic images demonstrating a hypointense lesion in T1-weighted MRI.

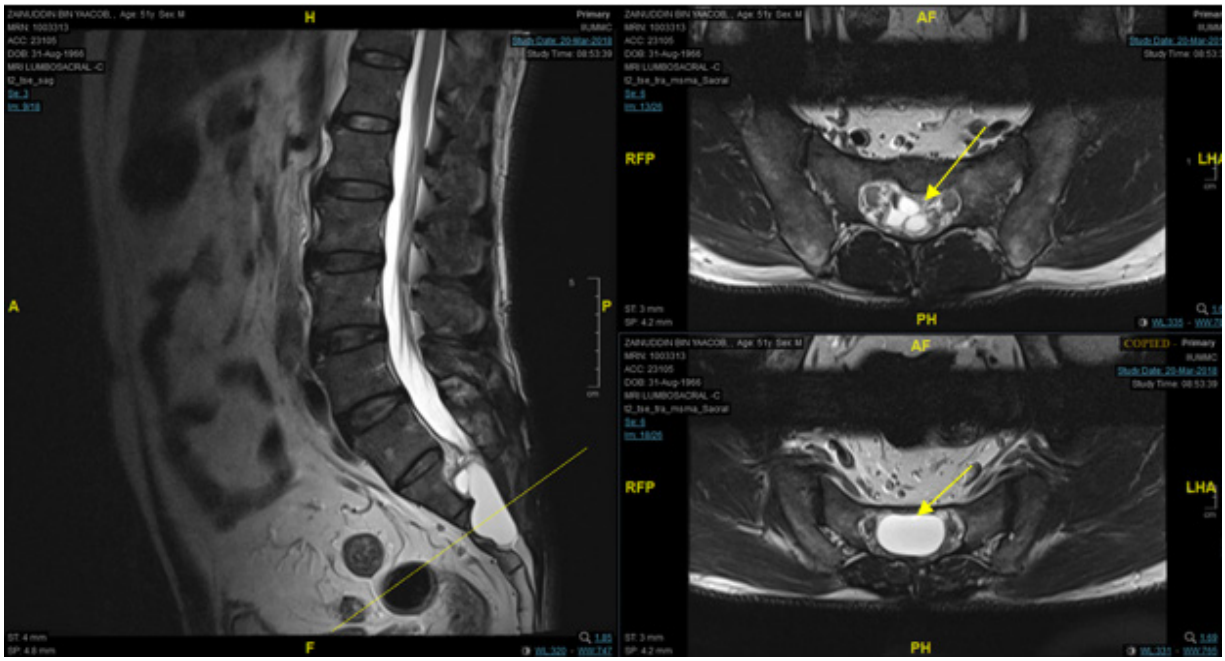

Figure 2 T2-weighted lumbosacral MRI images. Sagittal (a), axial (b, c) views show the well-defined multiloculated cystic structure which follows cerebrospinal fluid signal intensity (yellow arrow) at the S1 vertebra (b) and the cyst (yellow arrow) at S2 vertebra (c). Preoperative magnetic images demonstrating a hyperintense lesion in T2-weighted MRI.

A decompressive laminectomy over S1-S3, partial cystectomy, imbrication, fat graft packing, fabrication of Tarlov cyst, and duraplasty was performed. At surgery, laminectomy was done over 3 levels at the sacrum region, involving S1 – S3 using a Kerrison Rongeur, partial resection of the cyst wall was performed. An inlet was identified from the subarachnoid space (Figure 3), the adipose tissue was harvested from the abdomen earlier on was used to seal the subarachnoid connection and further reinforced with BioGlue (A composition of purified bovine serum albumin and glutaraldehyde) as a sealant to prevent cerebrospinal fluid fistula formation (Figure 4). The residual of the cyst wall was imbricated, and the obliteration was confirmed by a Valsalva manoeuvre. Subsequently, duraplasty was done using a dura patch to seal the defective area (Figure 5). No cerebrospinal fluid leakage postoperative, and hence spinal lumbar drainage was not inserted. The patient's lower back and buttock region pain, and S1 – S3 sensory disturbance distribution resolved postoperatively and remained asymptomatic 6 months later.

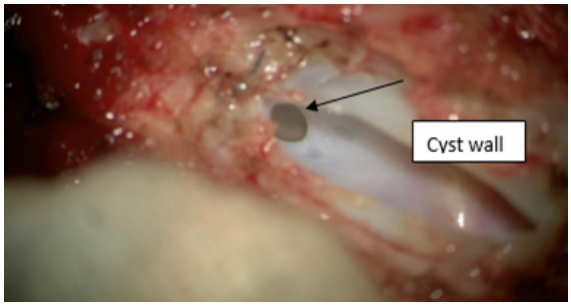

Figure 3 An inlet from the subarachnoid space was identified after partial resection of the cyst wall (black arrow)

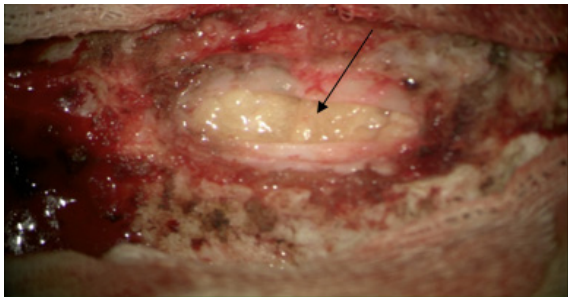

Figure 4 The subarachnoid linked to the cyst was sealed with adipose tissue (black arrow) and reinforced with BioGlue

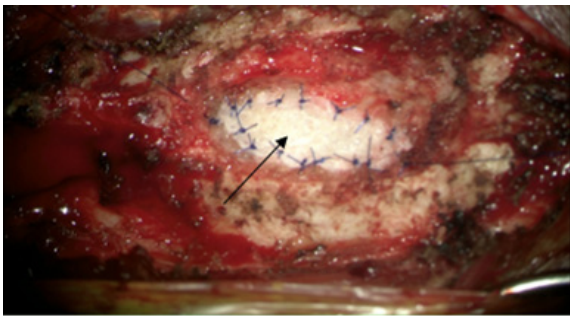

Figure 5 Duraplasty was performed using a dura patch (black arrow) to seal the defective area and was sutured using Prolene 5/0

DISCUSSION

Tarlov cysts are extrathecal cerebrospinal fluid-filled cavities in the perineurial recesses that are frequently found at the S2 and S3 levels. They are meningeal dilatation in between the endoneurium and perineurium in the spinal nerve root sheaths and are communicating with the subarachnoid space.

Tarlov discovered this perineural cyst in 1938, he postulated that the process of inflammation within the sheath of the nerve root leads to the formation of the cyst with the inoculation of fluid (Tarlov, 1938). Tarlov cysts are usually asymptomatic, only 1% may contribute to symptomatic Tarlov cysts (e.g., lower back/perineal pain, urinary and bowel incontinence, radiculopathic pain, and rarely infertility) (Tani et al., 2013). A ball-valve effect of the cerebrospinal fluid from the subarachnoid space has caused the growth of the Tarlov cysts which leads to symptomatic Tarlov cyst.

Varieties modalities of imaging tools are available to detect this type of lesion. CT, MRI and, myelography are the common tools used to detect Tarlov cysts. MRI has shown to be more efficient in investigating the relationship of the cyst with the surrounding soft tissues (Langdown et al., 2005).

Many neurosurgical treatment options proposed for symptomatic Tarlov cyst (Fibrin glue obliteration, partial cyst resection + imbrication, cyst fenestration only, partial cyst resection + imbrication, cyst wall clipping, cyst

fenestration + paraspinal muscle pedicle flap, imbrication + fat graft packing, partial cyst resection) (Sunday et al., 2018). The surgery aims to obliterate the connection with the subarachnoid space and prevent further communication with cerebrospinal fluid pathways, which will lead to a reduction of the size of the cysts and subsequently relieve the symptoms. In the literature available, the recurrent rate of surgical technique with cyst fenestration + paraspinal muscle pedicle flap had reported the highest recurrence percentage (74%) (Potts et al., 2016), followed by imbrication + fat graft packing (15%) (Weigel et al., 2016), partial cyst resection + imbrication (8%) (Xu et al., 2012), cyst fenestration alone (6%) (Smith et al., 2011), fibrin glue obliteration (Cantore et al., 2013) and cyst wall clipping (Patel et al., 1997) had reported the lowest recurrent rate of 0% respectively. Potts et al. (2016) reported after cyst fenestration technique in symptomatic Tarlov cysts had shown promising outcomes; however, it suffers from a high recurrent rate of 74%. The rest of the studies had reported comparatively low recurrent rates.

In this report, we decided to perform combined surgical techniques (partial cyst resection, imbrication, fat graft packing, and duraplasty) in this patient with recurrent Tarlov cysts. This combined approach has shown promising results. We would suggest further study by using combined surgical techniques in handling the cases of Tarlov cysts and to further analyze the efficacy and the rate of recurrence.

CONCLUSION

Many proposed surgical options are available for treating the symptomatic Tarlov cysts. Sacral laminectomy, partial cyst resection, imbrication, and adipose tissue packing to seal the subarachnoid space inlet reinforced with Bioglue with duraplasty in this case report appeared to be a viable and optimal surgical option.

CONFLICT OF INTEREST

The authors declare that they have no competing interests in publishing this case.

CONSENTS

Written consent was obtained from the patient to publish this case report. A copy of the written consent is available for review by the Chief Editor.

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SHORT COMMUNICATION

A Disease That Can Be Debilitating: Chronic Spontaneous Urticaria

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ABSTRACT

Chronic spontaneous urticaria is characterized by recurrent urticaria with or without angioedema for more than six weeks with no apparent external triggers. It affects up to one per cent of the general population and it is common in primary care settings or emergency services. Chronic spontaneous urticaria can be debilitating, difficult to treat, and frustrating for patients and doctors. Here, we described our experience of treating five patients with recalcitrant chronic spontaneous urticaria. Through this short communication, we would like to increase awareness of the general treatment approach to chronic spontaneous urticaria in primary care and specialist services.

INTRODUCTION

Chronic spontaneous urticaria is not triggered by identifiable factors. About one-half of patients with chronic spontaneous urticaria have associated angioedema which usually affects the cheeks, lips, periorbital areas, genitals, and extremities. Chronic spontaneous urticaria is a self-limiting disease in most patients with an average disease duration of two to five years. Up to 20 per cent of patients have persistent symptoms beyond five years (Van Der Valk et al., 2002). Here, we described our experience of treating five recalcitrant chronic spontaneous urticaria patients with up to four times the standard dose of second-generation antihistamine, leukotriene receptor antagonist, and subsequently omalizumab.

Treatment Experience

Patients' urticaria symptoms were evaluated by using the Urticaria Activity Score over seven days (UAS7 Score, Table 1).

Table 1 Urticaria Activity Score over seven days (UAS7 Score) (Zuberbier et al., 2018)

Score	Wheals	Pruritus
0	None	None
1	Mild (<20 wheals/ 24 hr)	Mild (present but not annoying or troublesome)
2	Moderate (20 – 50 wheals/ 24 hr)	Moderate (troublesome but does not interfere with normal daily activity or sleep)
3	Intense (50 wheals/ 24 hr or large confluent areas of wheals)	Intense (severe pruritus, which is sufficiently troublesome to interfere with normal daily activity or sleep)

Sum of score: 0 – 6 for each day is summarized over 1 week (maximum 42).

UAS7 < 7 may be evaluated as well-controlled, 7 – 15 as mild, 16 – 27 as moderate, 28 – 42 as severe activity urticaria.

Patient 1 was a 32-year-old female who had chronic spontaneous urticaria which was unresponsive to loratadine 10 mg QID and montelukast 10 mg ON. After the first dose of S/C omalizumab 300 mg, her chronic urticaria symptoms were generally improved (UAS7 score from 20 to 6). She received her second dose of omalizumab 300 mg after one month and she experienced partial hearing loss in both her ears after one week of injection. The symptom of partial hearing loss resolved after one month. Although a further improvement was seen in her UAS7 score (from18 to 6), omalizumab was discontinued as it was likely she developed drug-induced hearing loss after consultation with the ENT team. The patient's urticaria symptoms recurred about two months after stopping omalizumab, but it was generally better with a UAS7 score of 10 until now.

Patient 2 was a 49-year-old female with underlying endometriosis. She had chronic spontaneous urticaria which was unresponsive to bilastine 40 mg BD and montelukast 10 mg ON. After the first dose of S/C omalizumab 300 mg, her chronic urticaria symptoms had improved significantly (UAS7 score from 22 to 6). However, she developed worsening dysmenorrhea two weeks after the omalizumab injection. As a result, she declined subsequent doses of omalizumab. The patient's urticaria symptoms recurred after four weeks of stopping omalizumab with a UAS7 score of 12 to 14.

Patient 3 was a 24-year-old male with chronic spontaneous urticaria which was unresponsive to cetirizine 10 mg QID and montelukast 10 mg ON. He had to go to the emergency department once a month for IV hydrocortisone. He was given S/C omalizumab 150 mg monthly for two months and he responded well to the treatment (UAS7 score from 24 to 7). However, urticaria symptoms recurred six weeks after stopping omalizumab with a UAS7 score of 28.

Patient 4 was a 59-year-old female with chronic spontaneous urticaria which was unresponsive to loratadine 20 mg BD and montelukast 10 mg ON. She was given S/C omalizumab 150 mg for two doses and she responded well to the treatment (UAS7 score from 25 to 5). However, urticaria symptoms recurred eight months after stopping omalizumab with a UAS7 score of 15.

Patient 5 was a 49-year-old female with chronic spontaneous urticaria which was unresponsive to loratadine 10 mg QID and montelukast 10 mg ON. She was given S/C

omalizumab 150 mg monthly for one dose and her urticaria symptoms were controlled to date (UAS7 score from 2 to 5).

Some autoimmune disorders are more prevalent in patients with chronic spontaneous urticaria, for example, thyroid disorders, systemic lupus erythematosus, celiac disease, and Sjogren syndrome (Confino-Cohen et al., 2012; Kim et al., 2017; Lapi et al.,2016). All our patients with chronic spontaneous urticaria had no associated autoimmune symptoms, with normal thyroid function tests and negative ANA tests.

Evidence suggests that chronic spontaneous urticaria can have a substantial impact on patients' quality of life, mental health, and the ability to perform daily tasks (Maurer et al.,2017). The study has shown that some patients with chronic spontaneous urticaria had concurrent posttraumatic stress disorder resulting from past traumas and developed psychiatric comorbidity (Hunkin et al.,2012). A stepwise approach to treatment is recommended by major guidelines (Table 2) (Bernstein et al., 2014; Zuberbier et al., 2018). A difference between the 2018 international guidelines and the 2014 American practice parameters is the preference of the international guidelines to use a single antihistamine for up-dosing. Whereas the American guidelines suggest combining two different second-generation antihistamines when up-dosing.

Table 2 Comparison of 2018 International Guideline (left side) and 2014 American Guideline (right side) (Bernstein et al., 2014; Zuberbier et al., 2018)

	The EAACI/ WAO Guideline	**The AAAAI/ ACAAI Guideline**
Basic Treatment	Avoidance of triggers and relevant physical factors	
Step 1	Monotherapy with 2nd generation Antihistamine	Monotherapy with 2nd generation Antihistamine
↓	If inadequate control after 2 – 4 weeks or earlier	Assess for patient's tolerance and efficacy
Step 2	Increase 2nd generation Antihistamine dose (up to 4×)	One or more of the following: Dose advancement of 2nd generation antihistamine used in Step 1 Add another 2nd generation of antihistamine Add H2-antagonist Add Leukotriene receptor antagonist Add 1st generation antihistamine to be taken at bedtime.
↓	If inadequate control after 2 – 4 weeks or earlier.	Assess for patient's tolerance and efficacy
Step 3	Add-on to 2nd generation antihistamine: Omalizumab	Dose advancement of potent antihistamine as tolerated.
↓	If inadequate control after 2 – 4 weeks or earlier.	Assess for patient's tolerance and efficacy
Step 4	Add-on to 2nd generation antihistamine: Cyclosporin	Add other agents: Omalizumab or cyclosporin

EAACI, European Academy of Allergology and Clinical Immunology; WAO, World Allergy Organization. AAAAI: American Academy of Allergy, Asthma, and Immunology; ACAAI: American College of Allergy, Asthma, and Immunology.

Second-generation H1 antihistamines are first-line treatment, Up to 60% of patients remain symptomatic despite receiving H1 antihistamines at up to four times higher than the standard dose. Such patients may need additional treatments such as leukotriene receptor antagonists, cyclosporin, oral corticosteroid, or Omalizumab. Omalizumab is a monoclonal antibody directed against IgE, which was approved in the United States in 2014 for the treatment of patients 12 years of age and older with recalcitrant chronic spontaneous urticarial (Wu et al., 2015). Short-term systemic glucocorticoids may be considered to achieve temporary control of symptoms during severe exacerbations of urticaria that impair quality of life. Clinical trials have demonstrated that omalizumab significantly reduced (up to 44% to 52%) the UAS7 weekly itch and wheal scores in patients with chronic spontaneous urticaria not responsive to the standard dose of H1 antihistamines (Zhao et al., 2016). Even though omalizumab is generally well tolerated, adverse events have been reported. Common ones include headache, sinusitis, arthralgia, and local site reaction (Vestergaard et al., 2017). Omalizumab-associated hearing loss or dysmenorrhea has not been reported in the literature.

Patients with chronic spontaneous urticaria should be referred for specialist care in the following conditions:

1. Symptoms are not controlled with step 1 or require prolonged treatment with glucocorticoids.
2. An underlying disorder is suspected (such as autoimmune disorders, thyroid disorder).
3. Signs or symptoms suggest urticarial vasculitis, such as urticarial lesions that leave residual ecchymotic lesions or are associated with fever/ joint pain.

CONCLUSION

Patients with chronic spontaneous urticaria are often frustrated as it can significantly impair their quality of life. Apart from the treatment with an oral antihistamine, leukotriene receptor antagonist, or omalizumab, it is important to look for aggravating factors such as NSAIDs, heat, cold, sunlight, friction from clothing, alcohol, stress, concomitant infections, and menstruation. Understanding and learning to avoid those relevant aggravating factors are critical components of successful management.

CONFLICT OF INTEREST

The authors declare that they have no competing interests in publishing this article.

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CLINICAL QUIZ

Sudden Onset of Paraplegia With Rapid Progression to Tetraplegia in a Middle-Aged Man: What is the Diagnosis?

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QUESTION

A 58-year-old man, known case of diabetes mellitus, hypertension presented with sudden onset of bilateral lower limb weakness while resting, to the nearby medical centre. The weakness later progressed to involve bilateral upper limbs, leaving him tetraplegic, 3 hours from symptom onset. He denied chest or back pain. His electrocardiogram (ECG) revealed sinus rhythm, without any acute ischemic changes. There was no preceding febrile illness or injury. His case was referred to our centre with the impression of Guillain-Barre Syndrome (GBS).

He came to us, about 12 hours after the onset of weakness. Initial assessment revealed a flaccid tetraplegia man with modified medical council (MMC) power of 0/5 for all 4 limbs and generalised areflexia. Sensory modalities: pinprick and proprioception, were otherwise intact. His vital signs revealed blood pressure ranges of 100 – 106/ 60 – 70 mmHg, with bradycardia (heart rate of 55 – 60 beats/ min), afebrile with good oxygenation under room air. There was a loss of bulbo-cavernous reflexes, anal tone, and perianal sensation. He had urinary retention. These constellations of signs were consistent with spinal shock.

The cerebrospinal fluid (CSF) analysis revealed mildly raised protein of 0.66 g/l, with a cell count of one/mm3, CSF to serum glucose ratio of more than 0.6, and negative for microbiology analysis.

Magnetic resonance imaging (MRI) of his spine is shown in Figures 1 and 2.

Interpret the findings and suggest the provisional diagnosis.

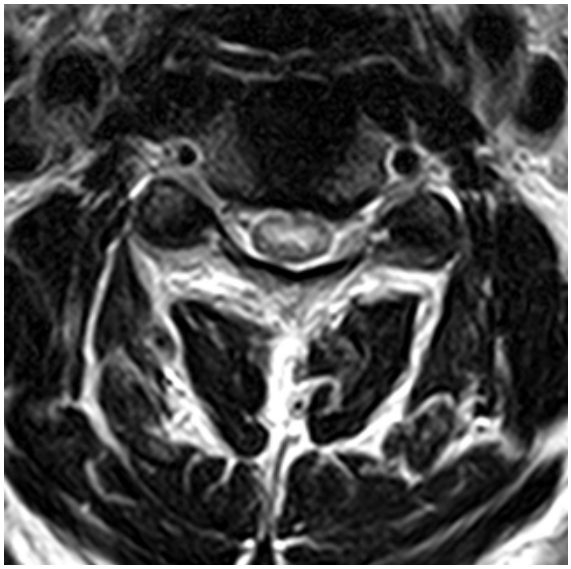

Figure 1 Axial T2WI MRI (magnified view) at the cervical cord level

Figure 2 Sagittal T2WI MRI Cervical cord

Please find out the answer in the next issue.

CONFLICT OF INTEREST

The authors declare that they have no competing interests in publishing this article.

CONSENTS

Written consent was obtained from the patients to publish the article (including images, case history, and data). A copy of the written consent is available for review by the Chief Editor.

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