VOLUME 1 : 2009

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International Journal of Collaborative Research on Internal Medicine & Public Health

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Senolytics and Cellular Senescence: The Road to the Clinic

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Received: 05-June-2022, Manuscript No. IJCRIMPH-22-73001; **Editor assigned:** 10-June-2022, PreQC No. IJCRIMPH-22-73001(PQ); **Reviewed:** 16-June-2022, QC No. IJCRIMPH-22-73001(Q); **Revised:** 24-June-2022, Manuscript No. IJCRIMPH-22-73001(R); **Published:** 30-June-2022, doi: 10.35248/1840-4529.22.14.6.368

Abstract

Many ailments and diseases appear to have interrelated and fundamental ageing processes at their foundation. Cellular senescence is one such mechanism, which involves a cell cycle stop in response to harmful stimuli. Senescent cells can appear at any time during life and, due to the numerous proteins they secrete, can have detrimental impacts on tissue function if they are persistent. Interventions against persistent senescent cells that destroy tissue have been proven in preclinical models to postpone, stop, or even reverse a variety of diseases. Accordingly, the development of small-molecule senolytic medicines that specifically eliminate senescent cells has resulted in potential methods for the prevention or treatment of a variety of diseases and age-related problems in people. In this Review, we explain the rationale for using senescent cells as a therapeutic target for diseases affecting people of all ages and talk about the most promising methods for putting small-molecule senolytics and other senescence-targeting interventions into clinical practise, including recent and ongoing clinical trials.

Keywords: Cellular senescence • Senolytic medicines • Respiratory symptoms

Introduction

The number of people who are older is rising gradually. By 2030, the World Health Organization (WHO) predicts that 1 individual in 6 individuals, or 2.1 billion people, would be older over 60. The majority of diseases that cause the majority of morbidity, death, and healthcare expenses in low-income, middle-income, and high-income nations are mostly predicted by chronological age. In children as well as adults, ageing can be accentuated at the etiologic sites of many acute and chronic disorders. In fact, essential ageing processes can start to take place even before conception, as is the case with older oocytes associated with Down syndrome. Cellular senescence is a key ageing mechanism that is receiving more and more attention. Senescent cells build up as people age and at the sites of many pathological conditions and diseases. Promising outcomes from preclinical investigations have aided transition to early-phase clinical trials testing the safety and efficacy of senolytics since the initial reports of senolytic medications in 2015, some of which have since been published. One important mechanism of ageing that is getting more attention is cellular senescence. As people age and at the locations of many clinical illnesses and diseases, senescent cells accumulate. Subsequently the initial reports of senolytic drugs in 2015, some of which have since been published, promising results from preclinical investigations have aided in the transition to early-phase clinical trials evaluating the safety and efficacy of senolytics. According to the Geroscience Hypothesis, several aspects of ageing, such as cellular senescence, tend to advance together and may be major factors in the pathophysiology of a number of diseases, aging-related dysfunction, and loss of resilience. The Geroscience Hypothesis is expanded upon by the Unitary Theory of Fundamental Aging Mechanisms, which asserts that therapies targeting one fundamental mechanism may also target the others. In experimental animal models of ageing and chronic diseases, interventions that target cellular senescence, for instance, have been shown to attenuate other fundamental ageing mechanisms, resulting in reduced inflammation, attenuated progenitor exhaustion, decreased fibrosis, and a partially restored microbiome. It is possible that multimorbidity could be reduced and health span increased by understanding and addressing cellular senescence and the other pillars of ageing rather than focusing on specific diseases that are downstream of fundamental ageing processes, with realisation of significant societal and financial benefits. In this Review, we examine the potential therapeutic value of senescent cells, the state of senolytic drug development, and the route to clinical implementation of senescent cell-targeting preventive and therapeutic approaches.

Cellular Senescence

After serially subculturing human fibroblasts, Hayflick and Moorhead published the first study on cellular senescence in 1961. Senescent cells, which are basically in an irreversible cell cycle halt but are still alive, can build up with age, especially in more frail people, and in the locations of many pathologies in experimental animals and people across the lifespan. Numerous stressors, such as DNA damage, cancerous mutations or oncogene activation, mitochondrial dysfunction, reactive metabolites, hyperoxia or hypoxia, proteotoxic stress, extracellular signals, infections, mechanical or shear stresses that cause cell deformation, resistance exercise, and substances secreted by other senescent cells, can cause cells to become senescent. Numerous such stresses trigger DNA damage response signalling, the *p53/p21CIP1/WAF1*, the p16INK4a/retinoblastoma protein, as well as other pathways. This causes cell cycle arrest and the emergence of a Senescence-Associated Secretory Phenotype (SASP). Those senescent cells with a proapoptotic SASP can survive despite the cytotoxic microenvironment they produce by upregulating pro-survival and antiapoptotic pathways like SRC kinases, the PI3K-AKT signalling pathway, Heat Shock Protein (HSP) pathways, serpines, mitochondrial pathways, or apoptosis regulator *BCL-2*-related proteins.

The senescent-associated secreted phenotype

Most cells going through senescence produce a SASP. This SASP includes pro-inflammatory, pro-apoptotic, and pro-fibrotic proteins in 30%–70% of senescent cells; some of these factors can induce previously unsenescent cells to become senescent both locally and at a distance in an endocrine manner. This proapoptotic SASP can have detrimental effects both locally and systemically due to senescent cell accumulation and persistence. Compared to proapoptotic, pro-inflammatory senescent cells, the remaining 30%–70% of senescent cells appear to include growth and other regenerative factors, which may reduce apoptosis, tissue damage, and fibrosis and even aid in tissue regeneration. Senescent cells can orchestrate tissue remodelling, trigger immune responses during infections or tissue injury, encourage parturition by releasing SASP factors, and promote clearance of those senescent cells with a pro-inflammatory SASP if they are transiently present. Immune cells can be drawn to, anchored to, and activated by both pro-apoptotic and pro-growth types of SASP.

Adverse impacts of persistent, proapoptotic SASP-expressing senescent cells

Senescent cells typically appear to be eliminated by natural killer cells and other immune cell types days to weeks after they originate. Senescent cells, however, can build up if a threshold burden of them is exceeded, possibly because proapoptotic SASP-expressing senescent cells drive the paracrine and endocrine spread of senescence at a rate that outpaces immune clearance of already-existing and newly-formed senescent cells. Senescent cell burden may continue to rise after it crosses this threshold, boosting senescent cell accumulation in a feed-forward loop while also contributing to tissue degradation, the onset or progression of numerous diseases, age-related disorders, and immunological dysregulation. This sterile inflammatory state can cause nearby and far-off non-senescent cells, such as progenitor cells, to malfunction, impairing tissue function and reducing the ability to regenerate. In line with this, persistent senescent cells have been linked to diseases like extracellular matrix degradation, fibrosis, and insulin resistance in adipose tissue, reduced muscle hypertrophy after resistance exercise, and impaired fracture healing in older people, as well as to the promotion of malignant transformation.

Senescent cells' SASP is not constant; it can alter over time and differs based on the type of cells that underwent senescence and the method used to cause it. SASP factors are created and how much of them are present can be controlled by the intracellular and extracellular environment. The proapoptotic, pro-inflammatory properties of the SASP can be exacerbated by persistent senescent cells, which appear to be particularly receptive to external cues like

Damage-Associated Molecular Patterns (DAMPs) and Pathogen-Associated Molecular Patterns (PAMPs).

Discovery and development of senolytic drugs

A hypothesis-driven, mechanism-based approach to drug development was used to find the first senolytic medications. It was assumed that these senescent cells rely on antiapoptotic, pro-survival pathways to prevent self-destruction because the 30%–70% of senescent cells with a proapoptotic, tissue-destructive SASP are themselves resistant to apoptosis. Senescent cells do exhibit overexpression of one or more Senescent Cell Antiapoptotic Pathways (SCAPs), according to the analysis of proteomic and transcriptome datasets. Similar to the mechanisms that shield some cancer cells, such as B cell lymphoma or chronic lymphocytic leukaemia cells, which also release tissue-destructive proapoptotic proteins but avoid going through apoptosis themselves, SCAP pathways protect specific cancer cells. 46 drugs that target SCAP pathways were found to be potentially senolytic by bioinformatic analysis. In order to accelerate the transition from the bench to the bedside, the first senolytic agents were purposefully chosen to be studied further because they: (1) target multiple SCAPs rather than using the conventional drug development strategy of one drug/one molecular target/one disease; (2) can be taken orally; (3) are natural products with well-known safety profiles; or are already approved by the US Food and Drug Administration (FDA) for other indications. High-throughput library screens and other techniques are increasingly being used to find second-generation senolytics. One strategy is based on the fact that many senescent cells have increased lysosomal mass and senescence-associated galactosidase activity; galacto-oligosaccharide-coated nanoparticles and galactosidase-activated prodrugs seem to kill at least some of these cells. Another strategy is based on the fact that some senescent cells have high levels of lysosomal activity, making them vulnerable to lysosomal ATPase inhibitors. At least some senescent cells rely on glutamine metabolism as a pH-buffering system because of ruptured lysosomal membranes; suppression of this metabolism makes the cells susceptible to death.

SASP inhibitors

Another therapeutic strategy for treating cellular senescence-related phenotypes or disorders involves suppressing the SASP without destroying senescent cells. By blocking the Nuclear Factor (NF)-B transcription factor, the JAK-STAT signal transduction pathway, the serine/threonine protein kinase mTOR, targets of the mitochondrial complex-1 or complex-4, or other pathways involved in the induction and maintenance of the SASP. SASP inhibitors can either directly or indirectly reduce the SASP of senescent cells. Inhibitors of NF-B can lower pro-inflammatory SASP cytokines and chemokines both *in vitro* and *in vivo*.

Conclusion

Senescent cell elimination has become a viable therapeutic approach for avoiding, postponing, or treating a variety of diseases and age-related dysfunction. Senolytics' promising preclinical results point to therapeutic and preventive options for postponing multimorbidity and lengthening life expectancy. While randomised controlled trials will determine the efficacy and safety of senolytic methods, immediate scientific and regulatory issues must be resolved if senolytics are to be employed in clinical settings. Finding dependable, sensitive, and specific gerodiagnostics—biomarkers that measure senescent cell abundance, the SASP, and senolysis as well as other pillars of ageing—should be a top focus. A possibility that needs to be experimentally tested and compared with predictive gerodiagnostics is the possibility of interventions modulating the SASP (including those that specifically upregulate or downregulate tissue-destructive factors versus growth factors) or topical senolytic agents, especially those that eliminate senescent cells with a proapoptotic SASP. Clinical advancement is hampered by the absence of WHO International Classification of Disease (ICD) codes for multimorbidity, sarcopenia, healthspan, or geriatric disorders. Such ICD codes would make it easier for the pharmaceutical sector to participate in regulatory approvals, epidemiological studies, the recording of conditions associated with basic ageing processes in hospital and insurance records, and physician and hospital reimbursement. To improve our understanding of basic ageing mechanisms and illness etiologies and to develop therapeutic options to lower multimorbidity and lengthen healthspan, it is necessary to look into any potential interdependencies among fundamental ageing mechanisms. One final word of caution is crucial. Although preclinical studies are encouraging, senolytics or SASP inhibitors should not be recommended for the over-the-counter or in clinical practise unless carefully controlled, rigorous clinical trials show their safety and effectiveness. While waiting for small-molecule senolytics to enter the clinic, findings from present and upcoming clinical studies will provide insightful information about the function of cellular senescence as a therapeutic target for age-related illnesses.

Cite this article: Miller R. Senolytics and Cellular Senescence: The Road to the Clinic. Int. J. Collab. Res. Intern. Med. Public Health. 2022, 14 (06), 001-002

Third-Dose Immunogenicity of the COVID-19 mRNA Vaccine in HIV-Positive Individuals

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Received: 06-June-2022, Manuscript No. IJCRIMPH-22-72977; **Editor assigned:** 10-June-2022, PreQC No. IJCRIMPH-22-72977(PQ); **Reviewed:** 18-June-2022, QC No. IJCRIMPH-22-72977(Q); **Revised:** 24-June-2022, Manuscript No. IJCRIMPH-22-72977(R); **Published:** 30-June-2022, doi: 10.35248/1840-4529.22.14.6.369

Abstract

We examined anti-RBD, micro neutralization assay, and IFN- production in 216 PLWH on ART with advanced disease receiving the third dose of an mRNA vaccine after a median of 142 days from the second dose in order to investigate the safety and immunogenicity of SARS-CoV-2 vaccine third dose in people living with HIV (PLWH). At least one adverse effect, usually a minor one, is seen in 68% of PLWH. Particularly when a heterologous combination with mRNA-1273 is used as the third shot, the humoral response after the third dose was strong and higher than that attained with the second. Cell-mediated immunity, however, does not change. Our findings suggest the third dose's utility for PLWH who are currently undergoing suppressive ART and who have significant immune dysregulation.

Keywords: SARS-CoV-2 • Vaccine • Reading problems

Introduction

According to data from the World Health Organization up until December 27th 2021, the COVID-19 pandemic caused more than 270 million confirmed illnesses and around 5 million fatalities. More than 7 million doses of effective SARS-CoV-2 vaccinations have been delivered worldwide, and they have proven to be a highly effective method of reducing the disease burden, especially in those who are at a high risk of contracting a severe COVID-192. Furthermore, real-world data indicate that an effective vaccination can prevent fatal illness even in the presence of variations of concern (VoCs), such as the Gamma and Delta variants. Recent studies have indicated that the vaccine effectiveness for the B.1.1.529 (Omicron) variant is much lower than that seen with the delta form, decreasing antibody-mediated neutralization and perhaps raising the risk of reinfections. Recent research has shown a considerable rise in neutralization against Omicron following a booster dosage, however this rise was less pronounced than that seen with ancestral type or Delta, pointing to the possibility of cross-reactivity between neutralizing antibody responses. Despite differences between studies, People Living With HIV (PLWH) appear to be at a high risk for negative clinical outcomes from COVID-19. There is some evidence for higher hospitalization and mortality rates, which may be related to low neutralizing antibody titers, which reflect a weakened immune response to the natural infection of SARS-CoV-2, the presence of additional comorbid conditions, and low socioeconomic status or occupational risk. These findings are in line with the hypothesis that HIV infection may make other viral agents, including influenza, more susceptible to a subpar serological response. In PLWH on stable ART and with CD4 counts greater than 350 cells/mm, only one randomized, phase 2/3 trial in the UK has characterized the immunogenicity to a prime-boost dosage of the chimpanzee adenovirus-vectored ChAdOx1-nCoV-19 vaccine as well as its persistence after 6 months. At 6 months, this follow-up analysis revealed a reduction in humoral and cell-mediated immunity, but there was no discernible difference from a cohort of HIV-uninfected people who had the same vaccination. Only a few observational studies on mRNA vaccines in PLWH have been conducted to date, and all of them demonstrated a satisfactory humoral and T cell immune response in PLWH on ART and with CD4 T cell counts above 200 cell/mm^3 after the primary vaccination cycle. However, no data were available regarding the efficacy and safety of additional or booster doses in the HIV-infected population, particularly in individuals with low CD4 count. We previously stated that mRNA vaccination can induce a strong humoral and cellular immune response against SARS-CoV-2 in the majority of PLWH receiving ART, especially in those with complete immune recovery after suppressive therapy, even though such response was noticeably worse in PLWH with current CD4 T-cell 200/mm^3 compared to those with>500 cell/mm^3 and HIV-uninfected controls. These results suggest that chronic persistent dysregulation in the ART-treated population may affect effector immune response to SARS CoV2 immunization. The Italian government approved the third dose of the anti-SARS-CoV-2 mRNA vaccine to be administered on September 10, 2021, to PLWH who had a CD4 T cell count below 200 cell/mm^3 and/or a history of AIDS at the time of their first dose. This study aimed to evaluate the association between immune response, current CD4 T cell count, and specific vaccination sequence, as well as to identify the reactogenicity and level of immunogenicity in PLWH following the third dosage, compare those levels to those achieved following the second dose.

Discussion

In this investigation, we discovered that in PLWH eligible for the third dosage who had already received the full mRNA 2-dose vaccination cycle, a third dose of the anti-SARS-CoV-2 mRNA vaccine generated a significant humoral and T specific cell response. It's interesting to note that the T cell-mediated response, neutralising antibodies, and anti-RBD IgG all increased significantly. An important point to note is that the amount of anti-RBD IgG, neutralising antibodies attained after the third dose was higher than what was seen one month after the second dose of the primary cycle. Our data cannot rule out a difference in the magnitude of response and risk of no-response when comparing participants with poor CD4 count recovery on ART (PCDR) with those with high CD4 count recovery on ART, despite the lack of a significant association between the current level of CD4 count and the response (HCDR). Comparing the results attained post-second dose with those shown post-third dose, however, suggested that the amount of T cell mediated response was more steady. Anti-RBD and nAb responses were comparable to those of the HIV Negative Control Group (HCWs), which were not noticeably different. The findings, however, contained strong support for a smaller mean difference in IFN-gamma between PLWH and controls. These findings are crucial because they demonstrate that PLWH appear to have a compromised T-cell mediated response relative to the general population, despite a strong response to a third dosage. These results appear to be comparable between HIV positive and HIV negative participants, which is in accordance with recent findings on the characterisation of the humoral and SARS-CoV-2 T-cell specific response in PLWH following a moderate COVID19. Additionally, we discovered a significant difference in terms of T-cell specific response in PLWH that was lower than that seen in the HIV negative control group, and we contend that the size of the naive CD4 T cell pool influences the overall magnitude of SARS-CoV-2-specific T cell responses. This suggests that insufficient immune reconstitution on ART may compromise immune responses to SARS-CoV-2 and vaccine effectiveness in PLWH. The observed increase in humoral response in our setting is also in line with the theory that the third dose induces a strong B cell memory response, which was previously induced by the primary vaccination series, and it emphasises the ability of the SARS-CoV-2 mRNA vaccines to stimulate an adequate humoral response. These findings may be important since they provide fresh information on PLWH's immune response to an additional mRNA vaccination. PLWH had lower surrogate virus neutralisation test response and a trend toward lower IgG response, especially among those with lower CD4$^+$ T-cell counts and who received the BNT162b2 vaccine (vs mRNA1273), according to a recent matched case-control study on humoral response to primary mRNA vaccination cycle in HIV positive and HIV negative individuals. This study highlights the need to identify groups that have reduced response to SARS-CoV-2 vaccination in order to set an ideal vaccinationComparing these response rates to those seen in other immunocompromised individuals, they are astounding. In people with Chronic Lymphocytic Leukaemia (CLL), the rate of anti-RBD response after a third dosage was 72%, and it was even lower when limited to patients receiving chemoimmunotherapy (60%). Only around 70% of patients receiving hemodialysis who did not respond well to the first two doses of the vaccine were able to produce effective antibody titres after the third dosage. Our results, however, are consistent with a recent report on immunogenicity in patients with solid and hematologic cancers. Additionally, in a different study, an immediate antibody response to booster administration of the BNT162b2 vaccine was seen in nearly all patients with solid organ tumours, including those who were receiving active systemic chemotherapy.

The third dose as well as the initial immunisation cycle were successful in boosting the Spike-specific T cell response. However, in contrast to the formation of antibodies, the T cell response induced by the third dosage was comparable to that brought about by the primary vaccination cycle, indicating that the first two doses are still sufficient to induce a completely T-cell immunisation. The additional third dose can significantly increase the T cell response, which decreased over time after the first two doses. After receiving their third dose of the vaccine, the majority of our PLWH who had severe immunodeficiency at the time of their first dose of the vaccine showed an anti-RBD IgG response (95.5%), nAbs response (86.3%), and T cell immunity (70%) that seems remarkable given the population's severe and persistent immunologic dysregulation, which is caused by a decreased T and B cell functionality brought on by lingering inflammation and immune-senescence processes. Given the patients' status as having chronic immunological dysregulation and the fact that depletion of viral-specific T and B cell clones is seen even in PLWH responders to antiretroviral therapy, the achieved responses are particularly impressive combinatorial antiretroviral therapy (cART). Although cART permanently suppresses HIV-RNA, restores $CD4^+$ T cells, and corrects HIV-related immunological dysfunction, a persistent immunopathology, such as that seen in HIV chronic illness, can impair the effectiveness of vaccination-induced immune responses. A third dosage had the best effect on our sample of advanced PLWH that had previously been activated by a full cycle immunisation. This study appears to indicate that successful cART can limit HIV replication and improve immunological function, even in individuals with low CD4 counts or those who have had AIDS-related illnesses. But more research is needed to completely understand how HIV-related immunosuppression affects how long vaccine-induced immunity lasts. Indeed, it's been said that the CD4 count is the first to appear. The CD4 T cells and the ongoing mild inflammatory milieu in chronic PLWH may inhibit the development of efficient and long-lasting memory B and T cell immunity. We found a significant difference in humoral response when comparing participants with poor CD4 count recovery on ART with those having a high CD4 count recovery, despite the fact that the data overall provided little evidence for an association between current level of CD4 count and response to vaccination. The results for the other replies also tended to favour those with PCDR over those with HCDR, while they were not statistically significant, perhaps due to insufficient statistical power. To address this issue, which is essential for properly designing the upcoming vaccine regimens, additional research is required. Our data are consistent with the findings of another recent study showing higher immunogenicity and significantly enhanced effectiveness of two doses of mRNA1273 compared with BNT162b2 and with the hypothesis that the observed higher vaccine response with the mRNA-1273 could be related to the additional week between administrations, higher vaccine dose, differences, or other factors, even though formal conclusions regarding the clinical significance of this observed difference cannot be made. Additionally, it has been demonstrated that the T cell response brought on by both vaccination and spontaneous infection is capable of effectively recognising the Omicron variation (70%–80% of CD4 and CD8 T cells cross-recognize Omicron), helping to protect against severe COVID-19. Therefore, by raising the titer of neutralising antibodies and producing a powerful and cross-reactive T cell response, vaccination in PLWH could considerably lower the chance of developing severe Omicron illness. Despite these drawbacks, the results reported here show that in PLWH who had advanced disease at the time of their first vaccination dose, administering a second dose of the SARS-CoV-2 mRNA vaccine at least four months after the first two doses resulted in noticeably higher levels of boosted immunity after initial course. These preliminary findings suggest to support the choice to administer a short-term third dosage to this subset of PLWH, even if more and larger trials are necessary to demonstrate the therapeutic benefit of the third dose.

Cite this article: Marino A. Third-Dose Immunogenicity of the COVID-19 mRNA Vaccine in HIV-Positive Individuals. Int. J. Collab. Res. Intern. Med. Public Health. 2022, 14 (06), 001-002

Visual-Spatial Attention Impairment in Reading-Challenged Kids

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Received: 06-June-2022, Manuscript No. IJCRIMPH-22-72750; **Editor assigned:** 10-June-2022, PreQC No. IJCRIMPH-22-72750(PQ); **Reviewed:** 18-June-2022, QC No. IJCRIMPH-22-72750(Q); **Revised:** 24-June-2022, Manuscript No. IJCRIMPH-22-72750(R); **Published:** 30-June-2022, doi: 10.35248/1840-4529.22.14.6.370

Abstract

Although visual-attentional skills may have a causal role in the development of reading skills, developmental reading difficulties (developmental dyslexia) have historically been primarily linked to auditory-phonological abnormalities. The orthographic processing of the letter string and the graphemic parsing that come before the grapheme-to-phoneme mapping may include visuo-attentional mechanisms. Here, we measured visuospatial attention in a sizable sample of primary school children (n=398) using a straightforward paper and pencil activity made up of three labyrinths. Our labyrinth task, which also controls for sensorimotor learning, primarily evaluates dispersed and focused visuospatial attention in contrast to visual search tasks that require visual working memory. Children with reading difficulties (n=58) displayed obvious visuospatial attention deficits compared to regular readers (n=340), which did not appear to be related to the motor coordination and procedural learning abilities required for this paper and pencil exercise. An effective reading rehabilitation programme should incorporate both auditory-phonological and visuo-attentional therapies, as visual attention is defective in roughly 40% of children with reading difficulties.

Keywords: Motor coordination • Neuro-developmental disorders • Reading problems

Introduction

Despite having an average IQ, teaching experience, and the absence of any overt sensory deficits, developmental dyslexia is a distinct reading issue. Developmental dyslexia is included as a potential result of a particular learning impairment in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Within the category of neurodevelopmental disorders, such as language disorder, attention deficit, and hyperactivity disorder, developmental coordination disorder, and autism spectrum disorder, the diagnosis of a particular learning disorder is frequently preceded or followed by additional diagnoses. According to the phonological core deficit theory, Reading Problems (RD) in kids with developmental dyslexia are caused by deficiencies in the ability to recognise and actively respond to spoken word sounds, which makes it difficult for them to learn the correct grapheme-to-phoneme mapping. Thus, the left temporoparietal junction, which is involved in auditory-phonological processing and recall of speech sounds, may be critical in the early stages of learning to read, when the development of the sub-lexical and lexical routes depends on grapheme-to-phoneme mapping. One of the best indicators of future reading ability is the amount of time it takes a prereading youngster to accurately and swiftly name a variety of well-known visual stimuli, or rapid automatized naming (RAN). In the same way that reading does, RAN tasks call for the following abilities: (i) attention to the stimuli; (ii) visual processes that are in charge of initial feature detection, discrimination, and stimuli identification; (iii) integration of visual information with stored orthographic and phonological representations; (iv) lexical processes, including access to and retrieval of phonological codes; and (v) organisation of articulatory output. Phonological awareness, visuospatial working memory, and RAN all appear to be reliable indicators of future reading development, according to longitudinal research. In the early stages of letter recognition and orthographic development, the frontoparietal network, which is engaged in visuo-attentional processing, may be extremely important. Stronger visual word form representations are possible thanks to effective visuospatial attentional extraction and selection skills. Scale-invariant gaze-centered letter detectors that jointly encode letter identification and letter location are the first step in the processing of orthographic data. These gaze-centered letter detectors respond in a manner that is concurrently influenced by visual acuity, crowding, and spatial attention. The right frontoparietal network is involved in attentional shifting (i.e., disengaging attentional focus) and scaling by combining signal-enhancing and noise-exclusion mechanisms (zoom-in and zoom-out of attentional focus). It is possible that the slow attentional shifting and altered perceptual noise-exclusion mechanisms that are frequently seen in children with developmental dyslexia are what cause the problems with quick stimulus-sequence processing. Graphemic parsing and letter-string processing require the following:(i)rapid and accurate deployment of visual attention along the letter strings; (ii) good abilities in global extraction and Spatio-temporal integration of visual information; (iii) a large visual-attention span; and (iv) a reduced visual crowding effect. Several longitudinal studies have confirmed that visuospatial attention abilities are good predictors of future reading skills. Importantly, visuo-attentional training seems to enhance reading abilities in kids with and without developmental dyslexia, supporting the idea that the frontoparietal attentional network is directly responsible for learning to read. The frontoparietal network is involved in many interactions with the environment, particularly in action recognition and action planning, in addition to attentional deployment, which is important for reading acquisition. It is interesting to note that visuo-attentional deficiencies are a hallmark of this neurodevelopmental illness, which affects children with developmental dyslexia at a rate of 16% to 70% comorbidity with a developmental coordination disorder. However, some longitudinal research on the potential connections between fine and gross motor skills and reading development have not produced consistent results, despite the evidence for the linkage between visuomotor and the attainment of reading and spelling skills. Particularly, when assessed with writing activities, some studies connected manual dexterity to upcoming reading abilities. A deficiency in sequential procedural learning (the capacity to learn a general task technique) has also been noted in children with developmental dyslexia, primarily in serial response time tasks. It's interesting to note that Lum and colleagues' meta-analysis revealed that the observed deficiency appears to be mostly related to a potential dysfunction in medial-temporal regions, which are involved in the processing of attentional spatiotemporal sequences. Additionally, children with developmental dyslexia display longer execution times while performing tasks that heavily require visuo-hand coordination, such as drawing a mirror. Although developmental dyslexia has been linked to visuomotor coordination impairments and procedural learning difficulties, a fundamental visuo-attentional deficit may also be a contributing factor.

Materials and Methods

Participants

The children that participated in our study totaled 398. The children attended primary school from the second to the fifth grade, where they were partially evaluated in schools in various Italian areas. The vision of children was normal or corrected to normal. There were no documented neurological issues or hearing problems. Using standardised word and pseudoword reading exercises, clinicians assessed children's reading skills. They were labelled as normal readers (TRs) or children with RD based on how well they performed on standardised word and pseudoword reading tasks. A child was labeled as having RDs if they performed at least two reading tests (word and/or pseudoword reading) at speeds and/or accuracy that were at least two Standard Deviations (SDs) lower than the average scores determined for a normative sample.

Cs labyrinth task

There are three sheets of labyrinths in the assignment. Eight by eight Cs are arranged in a square grid on each sheet with the four cardinal directions. The beginning is denoted by a red C with a triangle inside and the ending by a yellow circle. The participant was instructed to use the opening of the black C to draw a straight line from the triangle to the last circle, stopping at the adjacent C. Before the test, the kid was shown a sample sheet on which the test's administrator demonstrated how to do it, and a second sheet on which the participant performed a practise test. We consistently administered the three labyrinths in the same order so that we could examine the procedural learning abilities. The double administration of the identical labyrinth

path is expected to, in particular, result in an improvement in the second administration—an implicitly facilitative visuomotor impact at the core of the procedural learning mechanism. The attentional shifting index was similar between the first and second labyrinths, despite the fact that the first had 21 passages and the second had 36.

Discussion

A crucial factor in the growth of reading skills impeding orthographic processing is a visuospatial attention deficit. Using a straightforward paper-and-pencil activity that did not require auditory-phonological skills, we discovered a substantial difference in visuo-attentional ability between children with and without RDs. To attain the level of representation on which the grapheme-to-phoneme conversion process functions, computational models of reading presuppose a type of graphemic parsing. Visual information is divided into single letters and processed serially and one at a time. Regardless of how graphemic parsing is conceptualised, it necessitates first a focused visuospatial attention on each sublexical unit, followed by an efficient distributed visuospatial attention on the full letter-string. Visual search tasks also include concentrated and distributed visuospatial attention. Indeed, it has been shown that, in both shallow and deep orthographies, visual search abilities-without involving any phonological abilities-are good predictors of future reading skills. Additionally, visuospatial attention training through the use of action video games enhances both visual search efficiency and reading skills in both dyslexic and non-dyslexic children. Visual search tasks, on the other hand, necessitate not just distributed and concentrated visuospatial attention, but also working memory for the visual target and a precise match between the focused candidate item and the intended target. Children with dyslexia have poor visual working memory. Importantly, all of the components (Cs) that make up the visual paths in the labyrinth task are sequential targets that should be processed without using working memory, minimising the potential impact of visual working memory deficiencies on our visual task. Therefore, our results demonstrate that children with RD tend to have pure visuospatial attention impairments, regardless of visual working memory skills. Since reading experience may directly influence the development of visuospatial attention, Goswami has critically addressed the potential causal link between the acquisition of reading skills and visuospatial attention. The Cs labyrinth task required constant attentional reorientation in all directions, which ruled out the possibility that this difference was the result of a simple practise effect related to the habitual left-to-right attentional shifting trained during reading acquisition and consolidation. Instead, the reading direction in western orthographies is not exclusively left-to-right attentional shifting. Instead of a general speed of processing deficiency, the selective difference in execution durations between the two groups in the first and second labyrinth highlights the significance of strong visuospatial attention skills. Last but not least, individual data analysis revealed that approximately 40% of kids with RD had visuospatial attentional mechanisms that are compromised as measured by labyrinths 1 and 2, indicating that these kids have attentional dysfunction. It should be emphasised that increasing lateral visual noise and emphasising the particular orienting and zooming attentional mechanisms required during this straightforward paper and pencil task could improve the sensitivity of our labyrinth task to visuospatial attentional dysfunction. Therefore, the labyrinth task seems to be an effective method for identifying the presence of visuospatial attentional deficits in primary school students with RD and in kids with other neurodevelopmental disorders related to RD.

DD and developmental coordination problem frequently co-occur. The presence of a problem in this area may have an impact on performance in the Labyrinth task, which heavily relies on motor coordination abilities. However, the distinction between the first and third labyrinths could aid physicians in determining whether a particular challenge with visuospatial attention, motor abilities, or procedural learning may be present. The visuospatial attention deficit indexes, as demonstrated in the correlation section, regulate not only the procedural learning skills but also the visuomotor skills intrinsically captured in the performance of the third labyrinth (measured through the delta of the execution time between the first and second administration of the same labyrinth). Only having trouble with the first two labyrinths may signify a particular visual attentional problem. Finally, the potential contribution of IQ to the learning of reading was not taken into account in the current study. The correlation between IQ and reading progress in children with RD is contradictory, nevertheless. In conclusion, our research demonstrates that children with RD, as opposed to those who have conventional reading abilities, appear to have a visual attentional impairment that is unrelated to visual working memory or motor procedural learning. Our labyrinth test, in particular, highlights visual spatial attentional deficiencies that may affect both distributed and focused spatial attention in children with RD. The development of both lexical and sublexical reading pathways depends on these visual attentional mechanisms.

Cite this article: Chauhan D. Visual-Spatial Attention Impairment in Reading-Challenged Kids. Int. J. Collab. Res. Intern. Med. Public Health. 2022, 14 (06), 001-002

Parkinson's Disease Identification and Evaluation Using Nocturnal Breathing Signals with Artificial Intelligence

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Received: 04-June-2022, Manuscript No. IJCRIMPH-22-72993; **Editor assigned:** 06-June-2022, PreQC No. IJCRIMPH-22-72993 (PQ); **Reviewed:** 15-June-2022, QC No. IJCRIMPH-22-72993 (Q); **Revised:** 24-June-2022, Manuscript No. IJCRIMPH-22-72993 (R); **Published:** 30-June-2022, DOI: 10.35248/1840-4529.22.14.6.367

Abstract

As of right now, there are no reliable biomarkers for identifying Parkinson's Disease (PD) or monitoring its development. Here, using signals from nocturnal breathing, we created an Artificial Intelligence (AI) model to identify PD and follow its development. The model was assessed using data from numerous hospitals in the United States as well as numerous public datasets on a sizable dataset with 7,671 persons. On held-out and external test sets, the AI model can identify PD with an area under the curve of 0.90 and 0.85, respectively. The Movement Disorder Society Unified Parkinson's Disease Rating Scale, which is used to measure PD severity and progression, can also be used by the AI model. The AI model employs an attention layer that enables interpretation of its sleep and electroencephalogram predictions. Additionally, the model can detect breathing via radio waves that reflect off a person's body while they sleep to diagnose PD in the home environment touchless. Our study provides preliminary evidence that our AI model may be helpful for risk assessment before clinical diagnosis and shows the viability of objective, noninvasive, at-home evaluation of PD.

Keywords: Parkinson's disease • Disorder • Respiratory symptoms

Introduction

The world's fastest-growing neurological condition is PD1. As of 2020, more over 1 million Americans lived with PD, placing a$52 billion annual economic burdens on society. No medication has been able to halt or reverse the disease's course thus far. The absence of reliable diagnostic biomarkers is a major obstacle in the development of PD medications and disease management. The disease is typically diagnosed based on clinical symptoms, related mainly to motor functions such as tremors and rigidity. However, motor symptoms typically don't show up until years after the disease first manifests, which delays diagnosis. New diagnostic biomarkers are therefore desperately needed, especially ones that can spot the disease before it progresses too far. Additionally, there are no efficient indicators for determining how the disease progresses over time. Today, PD progression is evaluated by the patient or by a doctor using a qualitative rating system. A questionnaire called the Movement Disorder Society Unified Parkinson's Disease Rating Scale is typically used by clinicians (MDS-UPDRS). The MDS-UPDRS lacks sufficient sensitivity to detect subtle changes in patient status and is semi-subjective. In order to report changes in MDS-UPDRS with sufficient statistical confidence, PD clinical studies must extend for several years, which raises costs and slows down development. There are a few putative PD biomarkers that have been studied in the literature, and among these, cerebrospinal fluid, blood biochemistry16, and neuroimaging show good accuracy. These biomarkers are not appropriate for routine testing to provide early diagnosis or continuous tracking of disease progression because they are expensive, invasive, and require access to specialised medical facilities. As early as 1817, James Parkinson's research found a connection between PD and respiration. Later studies that revealed respiratory muscle weakness, sleep breathing issues, and degeneration in breathing-controlling brainstem regions further supported this connection. Further evidence that the breathing characteristics may be useful for risk assessment before clinical diagnosis comes from the fact that these respiratory symptoms frequently appear years before clinical motor signs. Here, we offer a novel AI-based method for diagnosing Parkinson's Disease (PD), estimating disease severity, and monitoring the course of the disease over time utilising nocturnal breathing. A breathing belt worn on the person's chest or abdomen can be used to gather one night's worth of breathing signals, which the system uses as input. As an alternative, the breathing signals can be obtained without the need of wearable technology by sending out a low-strength radio signal and observing how it reflects off the subject. This model's learning of the auxiliary task of predicting the person's quantitative electroencephalogram from nocturnal breathing, which prevents the model from overfitting and aids in reading the model's output, is a crucial aspect of its design. Our approach intends to create an objective, undetectable, affordable, and repeatable digital biomarker for diagnosis and progression that can be tested in the patient's home.

Results

Datasets and model training

The Mayo Clinic, the sleep lab at Massachusetts General Hospital (MGH), observational PD clinical trials funded by the Michael J. Fox Foundation (MJFF) and the NIH Udall Center, an observational study conducted by the Massachusetts Institute of Technology (MIT), and public sleep datasets from the National Sleep Research Resource, such as the SlEEP dataset, are some of the sources of the large and diverse dataset we use (MrOS). The breathing belt datasets and the wireless datasets were separated into two groups. The first group employs a breathing belt to monitor the subject's breathing throughout the night and is derived from polysomnography (PSG) sleep research. The second group uses a radio device to contactless capture nighttime breathing. The radio sensor is installed in the user's bedroom, where it monitors radio reflections from the surroundings to identify the breathing signal. Only one or two nights per participant are included in the breathing belt datasets, and neither MDS-UPDRS nor Hoehn and Yahr (H&Y) scores are present. The wireless datasets, on the other hand, contain longitudinal data for up to a year as well as MDS-UPDRS and H&Y scores, enabling us to confirm the model's predictions of PD severity and its development. When testing on the wireless datasets, we restrict ourselves to the PD patients and their age-matched control subjects because some of the people in the datasets are rather young (for example, in their 20s or 30s). The mean value for the control group is applied to any missing MDS-UPDRS or H&Y scores in the control participants. The neural network was not tested on the same subjects that were used for training. For PD identification, we used k-fold cross-validation (k=4), and for severity prediction, we used leave-one-out validation. By using data from other medical facilities to train and test the model, we were also able to evaluate cross-institution prediction. A final test was the only time the Mayo Clinic data was used, and it was maintained as external data and never accessed during development or validation.

Evaluation of PD diagnosis

We further explored whether merging multiple nights from the same person might increase accuracy. Since each subject has multiple nights, we use the wireless datasets (mean (SD) 61.3 (42.5)) and compute the model prediction score for each night. The person is deemed to have PD if their PD prediction score is more than 0.5, which ranges from 0 to 1. As the result of the final diagnosis, we use the median PD score for each participant. Next, we determine how many nights are required to reach a high test-retest reliability. Using the wireless datasets, we average the prediction across several nights within a time range to determine the test-retest dependability. According to the findings, dependability increases when we use multiple nights from the same subject and only requires 12 nights to reach 0.95 (95% CI (0.92, 0.97)).

Generalization to external test cohort

We validated our AI model on an external test dataset (n=1,920 nights from 1,920 subjects, out of which 644 have PD) from an independent hospital not involved during model development in order to evaluate the generalizability of our model across different institutions with different data collection protocols and patient populations.

An AUC of 0.851 was reached by our model. The results show that our model can generalise to a variety of data sources from organisations that were not exposed during training. By testing the model on data from one institution while training it on data from other institutions other than the test institution, we were able to assess the performance of cross-institution prediction. The model obtained a cross-institution AUC of 0.857 on SHHS and 0.874 on MrOS for breathing belt data. Cross-institution performance for wireless data was 0.892 on MJFF, 0.884 on Udall, 0.974 on MGH, and 0.916 on MIT. These findings demonstrate the model's exceptional accuracy on data from sources it was not exposed to during training. Therefore, the accuracy is not attributable to the misattribution of institution-related information to the disease or to the exploitation of institution-related information.

Evaluation of PD severity prediction

The MDS-UPDRS is currently the most widely used tool for assessing the severity of PD, with higher scores indicating more profound impairment. Both patients and doctors must put forth effort in order to evaluate MDS-UPDRS: patients are required to physically visit the clinic, and evaluations are carried out by qualified clinicians who classify symptoms using quasi-subjective criteria. By examining the patients' nighttime breathing at home, we test our model's capacity to generate a PD severity score that closely resembles the MDS-UPDRS. Each patient has many nights of measurements, and we use the wireless dataset when MDS-UPDRS evaluation is available (53 subjects, 25 PD subjects with a total of 1,263 nights, and 28 controls with a total of 1,338 nights). We contrast the baseline MDS-UPDRS results with the model's median prediction, which was calculated across the nights starting one month after the subject's baseline visit.

PD risk assessment

Since respiration and sleep are affected early in the progression of PD4, we believe that our AI model may be able to identify people with PD before they are officially diagnosed. We used the MrOS dataset, which contains breathing and PD diagnoses from two different visits separated by roughly six years, to assess this capability. The participants we looked at are referred to as the "prodromal PD group" (n=12) since they developed PD by their second visit but not by their first. We choose individuals from the MrOS dataset who did not receive a PD diagnosis during either the initial visit or the second appointment, which took place six years later, to serve as the "control group."

PD disease progression

MDS-UPDRS, which is semi-subjective and has insufficient sensitivity to detect subtle, gradual changes in patient status, is currently used to assess the development of Parkinson's disease. Therefore, before changes in MDS-UPDRS can be reported with appropriate statistical certainty, PD clinical trials must persist for a number of years, which poses a significant obstacle to medication development. Clinical trials for PD might be shortened by a progression marker that detects statistically significant changes in disease status over brief periods. We used the data from the baseline, the month after the month-6 visit, and the month after that to compute the median MDS-UPDRS prediction in order to determine the change in the predicted MDS-UPDRS. The median at baseline was then deducted from the median at month six. The same process was used again to calculate the difference in prediction between month 12 and baseline.

The estimates of changes in MDS-UPDRS made by the model over the same periods, however, are statistically significant. Our model's ability to combine measures from several nights is a significant factor in its ability to attain statistical significance for progression analysis while the clinician-scored MDS-UPDRS cannot. Any measurement contains some noise, whether it is the model-predicted MDS-UPDRS or the clinician-scored MDS-UPDRS. One can lower the noise and increase sensitivity to illness progression over a brief period by combining a lot of samples. Because the measurements may be repeated every night without causing any additional burden to the patients, this is possible for the model-predicted MDS-UPDRS. It is not practicable to ask the patient to return to the clinic every day to repeat the MDS-UPDRS test, thus one cannot do the same for the clinician-scored MDS-UPDRS. In the same way, as clinician-scored MDS-UPDRS failed to reach statistical significance, the model-predicted MDS-UPDRS would also fail to follow progression over a single night.

Discussion

This study offers proof that AI can recognise PD patients based on their nighttime breathing patterns and can properly determine the severity and course of the disease. We were able to validate our results in a separate external PD group, which is significant. The outcomes indicate the promise of a fresh digital biomarker for Parkinson's disease. This biomarker possesses a number of useful qualities. It functions as a biomarker for progression and diagnosis. Since it is objective, neither the subjectivity of the patient nor the therapist affects it. It is simple and non-intrusive to measure in the subject's home. Furthermore, measurements can be taken each night without touching anything by using wireless signals to track respiration. Our findings have a number of ramifications. First, by potentially decreasing the cost and length of PD clinical trials, our strategy could speed up the development of new drugs. The typical price and length of PD drug development are roughl 1.3 billion and 13 years, respectively. As a result, few pharmaceutical companies are interested in developing novel treatments for PD13. Since PD is a slowly-progressing disease, it takes several years for present tools to identify progression because they are imprecise and unable to detect minor changes. Our AI-based biomarker, in contrast, may be more sensitive to PD's gradual changes than previously thought. This can assist cut down on costs, expediting progress, and shortening clinical trials. Since measures may be taken at home with no expense to the patients, our approach can also increase patient recruitment and decrease churn. Second, roughly 40% of those with PD are not currently being treated by a PD expert. This is because people with PD are geographically dispersed and have difficulty going to such centres due to old age and poor mobility, whereas PD specialists are concentrated in medical centres in urban areas. Additionally, our study has several drawbacks. A nonhomogeneous disease, PD has numerous subgroups. We did not investigate the various PD subtypes or if our technique is equally effective with each subtype. The fact that the preclinical diagnosis and progression analyses were only validated in a small number of subjects is another drawback of the article. Future research involving bigger populations will be necessary to further support those findings. Additionally, even though we have demonstrated that our system can distinguish between Parkinson's disease and Alzheimer's disease, we did not test if our model can distinguish between Parkinson's disease and other, more widespread neurological disorders. Even though we evaluated the model across institutions and using independent datasets, more research may be able to use a wider variety of institutions and datasets.

Cite this article: Harper V. Parkinson's Disease Identification and Evaluation Using Nocturnal Breathing Signals with Artificial Intelligence. Int. J. Collab. Res. Intern. Med. Public Health. 2022, 14 (06), 001-002

Awareness, practice and factors influencing birth preparedness and complication readiness among women attending antenatal clinic at University of Calabar Teaching hospital (UCTH), Calabar, Cross River state, Nigeria

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Received: 22-June-2022, Manuscript No. IJCRIMPH-22-67356; **Editor assigned:** 23-June-2022, PreQC No. IJCRIMPH-22-67356(PQ); **Reviewed**: 24-June-2022, QC No. IJCRIMPH-22-67356(Q); **Revised**: 25-June-2022, Manuscript No. IJCRIMPH-22-67356; **Published**: 02-July-2022 doi: 10.35248/1840-4529.22.14.6.366

Abstract

Background: Birth preparedness involves a collaboratory efforts between the couple, family and healthcare professionals to have a successful antepartum, intrapartum and postpartum period.

Purpose: This study assessed awareness, practice and factors influencing birth preparedness and complication readiness among women attending antenatal clinic at University of Calabar Teaching Hospital (UCTH), Calabar, Cross River State, Nigeria.

Methods: Cross-sectional descriptive survey design was used for the study. A sample size of two hundred and thirty-eight (238) pregnant mothers utilizing maternal and child health service at UCTH, Calabar, random sampling technique was adopted, structured questionnaire was adopted for the instrument. Data collected were analyzed using descriptive charts, frequencies, tables and percentages. The hypothesis was tested for significance at 0.05 level, using Chi-square (X2) analysis.

Results: The result of the study showed that large proportion (73.5%) respondents have high level awareness of putting intervention in place for abnormal and obstructed Labour, while (26.5%) have low awareness. Majority (50.4%) respondents have high level practice, 39.1% have moderate practice, while 10.5% respondents have low practice. There is a statistical relationship between the level of awareness and practice of birth planned child birth as calculated value of 23.4 is higher than the P-value of 5.99 at 0.05 level of significant at 2 degree of freedom.

Conclusion: Adequate awareness and interventions put in place in case of slow progress of labour is an effective way of preventing maternal mortality.

Keywords: Chi-square • Birth preparedness and Complication readiness • Retained Placenta

Introduction

Birth Preparedness and Complication Readiness (BPCR) is a process of planning for normal child birth and putting in place recommended interventions' that is require in case of abnormal situation associated with labour this enhance preparation as well as its readiness towards any likely occurrence obstructed labour. This involves a collaboratory efforts among the couple, family members and healthcare professionals to have a good outcome before, during and after child birth period. Birth preparedness is a strategy to promote the timely use of trained health professional during childbirth, booked at hospital close to you with adequate maternal and child health services, setting out money for unexpected outcome during labour, movement to the hospital during unset of labour and unplanned situation that may arise during child birth and having blood donors in case of emergency [1]. Couples who take actions to receive care before the onset of pregnancy and completely attend all maternal and child health services and take recommended action toward child delivery, the pregnant mothers will receive maternal and care services on time without any period abnormal changes at labour [2]. Obstructed labour preparation raises awareness of abnormal changes during pregnancy and period of delivery, such as abnormal separation of placenta, blurred vision, oedema, protein urea, absent of fetal movement, prolong labour, retained placenta [3].

Pregnancy and childbirth sometime accompanied with unforeseen circumstance which can be life-threatening which most time lead to the death of mothers and neonate, particularly among mothers in low-income nations of the world. The causes of death during childbirth are view from different perspective including inability to identify abnormal changes in pregnancy; inability to report to health professional on time for adequate care, inability to come to hospital on time due to poor road network especially developing nations of the world like Nigeria and inability of health professional to attend to pregnant women on time due to inadequate resource and lack of skilled birth attendant at the point of delivery. Delays in receiving care may result from unprofessional conduct of healthcare professional, inadequate resources and recommended obstetric machines, a lack of healthcare professional and poor skills attendance [4]. These delays should be addressed at individual level, family level, community level, health providers, health facility and policy makers' level to ensure women and newborns receive appropriate, effective and timely care. The role of healthcare professionals is to educate couples attending ante-natal care about the importance of BPCR, the elements of BPCR and the abnormal changes during pregnancy and childbirth as well as anticipate factors that may cause any of the delays, develop a birth plan with the couple, it is therefore the interest of the researcher to assess the awareness, practices and factors influencing birth preparedness and complication readiness among couple attending antenatal clinic in UCTH, Calabar.

Material and Methodology

Cross-sectional descriptive survey design was used for this study. The setting of this study is University of Calabar Teaching Hospital (UCTH), Calabar. UCTH Calabar facility is located in Calabar municipality of Cross River State, Nigeria. Calabar lies between longitudes 8`18`00`E to 8`24`00E and latitudes 4`54`00N to 5`04`00E. It has an area of 406 km^2 and a population of 371,022 as at 2006 census. University of Calabar Teaching Hospital (UCTH) is used for teaching medical, nursing, medical laboratory science, radiography students and also students from other health related courses. It provides specialist clinical services as well as promotion of scientific evidence-based care through research. The hospital is made up of 25 wards and units and 923 beds [5].The sample of this study comprised 238 married pregnant mothers utilizing maternal and child health services at UCTH, Calabar. The sample size was calculated using thirty percent (30%) of the population of married pregnant mothers (794) utilizing maternal and child health services at UCTH, Calabar. The sampling technique used to select rspondents for this study was a simple random sampling technique. The instrument of data collection is a structured questionnaire which was administered to study participants using face to face method. Data was collected using person to person's administration of questionnaire to the participants. Data were analyzed using inferential and descriptive statistics and presented using frequencies, percentages, tables and descriptive means [6]. The hypothesis was tested using Chi-square analysis.

Results

Table 1. Socio-Demographic Data.

Variables	Frequency	Percentage (%)	Mean (X)
Age:			
Below 21	34	14.3	35
21 - 30	72	30.3	
31- 40	88	37	
41 - 50	44	18.4	

Marital status		
Married	175	73.5
Single	44	18.5
Divorced	11	4.6
Widow	8	3.4
Educational Qual.		
Primary education	22	9.3
Secondary education	141	59.2
Tertiary education	75	31.5
Occupation		
Civil servant	88	37
Unemployed	37	15.6
Business/traders	81	34
Artisans	32	13.4
Religion		
Christians	218	91.5
Muslims	6	2.5
African traditional religion	12	5
No of Children		
None	29	12.2
44563	86	36.1
44624	71	29.8
5 & above	52	21.8

The results of Socio-demographic variables presented in Table 1 revealed that most, 88 (37.0%) respondents within the ages of 31 years-40 years; 72 (30.3%) respondents were between 21 years-30 years; 44 (18.4%) respondents were within the ages of 41 years-50 years; while 34 (14.3%) respondents were below 21 years. Regarding the marital status, majority of the respondents, 175 (73.5%) respondents were married, single respondents were 44 (18.5%); divorcees were 11 (4.6%), while 8 (3.4%) respondents were widows [7]. Also, most of the respondents 141 (59.2%) had secondary education. those who had tertiary education were 75 (31.5%), while 22 (9.3%) respondents attended primary education. Eighty-eight 88 (37.0%) respondent were civil servants. 81 (34.0%) were into business and trading, 37 (15.6%) respondents were unemployed, while 32 (13.4%) respondents were artisans. In addition, majority of the respondents, 218 (91.5%) were Christians, 6 (2.5%) were Moslems, while 12 (5.0%) respondents were African traditional religion worshippers. Lastly, most 86 (36.1%) of the respondents had 1 children-2 children, 71 (29.8%) respondents had 3-3 children, 52 (91.5%) respondents had 5 children and above, while 29 (12.2) respondents had had no children yet [8].

Table 2. Summary of responses to items on level of birth preparedness and complication readiness among women attending antenatal clinic at UCTH, Calabar.

Statements	**Responses**					
	Agreed	**%**	**Disagreed**	**%**	**Σ**	**(X)**
Birth preparedness and complication readiness requires a pregnant woman to know her expected date of delivery.	181	76.1%	57	23.9%	419	1.76
A pregnant woman prepared and ready for birth complication should be aware that labour can start before due date.	176	73.9%	62	26.1%	414	1.74
Pregnant woman should make arrangement for transportation to hospital in case labour starts unexpectedly.	180	75.6%	58	24.4%	418	1.76
Vaginal bleeding and loosing liquor during pregnancy are danger signs that a pregnant woman should be aware of.	172	72.3%	66	27.7%	410	1.72
Swelling of face, ankle and feet are danger signs that a pregnant woman should report to midwives	162	68.1%	76	31.9%	400	1.68
When performing a breast self examination a woman should stand without a top and brazier in front of a mirror, using her right hand to examine her left breast and her left hand to examine her right breast	158	66.4%	80	33.6%	396	1.66
Total mean±(SD) score = 10.3						
Decision: Mean (X) ± SD score<1.5=low awareness, while 1.5 & above = high awareness						

Results in Table 2 revealed that majority, 181 (76.1%) participants are aware that birth recommended interventions requires a pregnant woman to know her expected date of delivery, but 57 (23.9%) respondents are not aware. One hundred and seventy-six (73.9%) respondents were aware that a pregnant woman prepared and ready for birth complication should be aware that labour can start before the due date, but 62 (26.1%) respondents were not. Also, 180 (75.6%) respondents were aware that pregnant woman should make arrangement for transportation to hospital in case labour starts unexpectedly, but 58 (24.4%) respondents were not aware [9]. Furthermore, 172 (72.3%) respondents were aware that vaginal bleeding and loosing liquor during pregnancy are danger signs that a pregnant woman should not take lightly, but 66 (27.7%) respondents were not. Again, 162 (68.1%) respondents were aware that swelling of face, ankle and feet are danger signs that a pregnant woman should report to midwives, but 76 (31.9%)

respondents were not aware. Lastly, 158 (66.4%) respondents were aware that birth preparedness and complication readiness entails that a pregnant woman saves money in case of emergency, but 80 (33.6%) respondents were not aware. In addition, the table showed that the total mean score obtained by the respondents is 10.3 out of 18.0. The highest mean score per item is 1.76 out of 3.0, and it was obtained on awareness of a woman's expected date of delivery. The lowest mean score per item is 1.66 out of 3.0, and it was obtained on awareness of saving money in case of emergency. This is followed by a mean score of 1.68 which is obtained on awareness of swelling of face, ankle and feet as danger signs that a pregnant woman should report to midwives.

Table 3. Factors affecting birth preparedness and complication readiness among couples attending antenatal clinic at UCTH, Calabar.

Statements	Responses					
	Agreed	%	Disagreed	%	Σ	(X)
The nearby health facility is very far from my place of residence making it difficult for me to access antenatal care	167	0.702	71	0.298	405	1.7
Lack of support/ assistance from family members, relative and friends makes it difficult for me to prepare and get ready for birth and complication.	188	0.79	50	0.21	426	1.79
Lack of financial support from my husband prevents me from practicing birth preparedness and complication readiness.	175	0.735	63	0.265	413	1.74
Religious and cultural beliefs make it difficult to practice birth preparedness and complication readiness.	52	0.218	186	0.782	290	1.22
Lack of awareness is a barrier to effective implementation of birth preparedness and complication readiness.	193	0.811	45	0.189	431	1.81
Poor inter-personal relationship between midwives and pregnant women makes it difficult for the women to prepare and get ready for birth and complication.	117	0.492	121	0.508	355	1.49
Total mean ± (SD) score = 9.75						
Decision: Mean (X) ± SD score <1.5=low awareness, while 1.5 & above= high awareness						

Results in Table 3 revealed that majority, 167 (70.2%) of the respondents agreed that the nearby health facility is very far from my place of residence making it difficult for me to access antenatal care, but 71 (29.8%) respondents did not. One hundred and eighty-eight (79.0%) respondents asserted that lack of support and assistance from family members, relative and friends makes it difficult for them to prepare and get ready for birth and complication, but 50 (21.0%) respondents did not. Also, 175 (73.5%) respondents agreed that lack of financial support from their husband prevents them from practicing birth preparedness and complication readiness, but 63 (26.5%) respondents disagreed. Furthermore, 52 (21.8%) respondents reported that religious and cultural beliefs make it difficult for them to practice birth preparedness and complication readiness, but 63 (26.5%) respondents did not. Also, 193 (81.1%) respondents reported that negative perception about breast cancer is responsible for low awareness and practice of breast self-examination, but 45 (18.9%) respondents did not. Lastly, 117 (49.2%) respondents stated that religious believes about diseases like breast cancer affects the level of breast self-examination among women of child bearing age, but 121 (50.8%) respondents did not. In addition, the table revealed that the total mean score obtained by the respondents is 9.75 out of 18.0. The highest mean score per item is 1.81 out of 3.0, and it was obtained on negative perceptions about breast cancer. This is followed by a mean score of 1.79 which is obtained on negative attitude about practice of breast self-examination. The lowest mean score per item is 1.22 out of 3.0, and it was obtained on low education. This is followed by a mean score of 1.49 which is obtained on religious beliefs about breast cancer [10].

Table 4. Chi-square (X^2) analysis of relationship between the level of awareness and practice of birth preparedness and complication readiness among couples attending antenatal clinic at University of Calabar Teaching Hospital (UCTH), Calabar (N=238).

Awareness BPCR	Practice of BPCR			Total	df	Sig.	X^2 Crit	X^2 Cal	Decision
	High	Moderate	Low						
High	85	74	16	175	2	0.05	5.99	23.4	Rejected
Low	35	19	9	63					
Total	120	93	25	238					
Significant at 0.05; df=1, X^2 Crit=5.99; X2 Cal=23.4									

The result Chi-square (X^2) analysis in Table 4 revealed that the calculated value of 23.4 is higher than the critical value of 5.99 at 0.05 level of significant with 2 degrees of freedom. This implies that the result is significant; therefore, the null hypothesis which stated that there is no significant relationship between the level of awareness and practice of birth preparedness and complication readiness among couples attending antenatal clinic at University of Calabar Teaching Hospital (UCTH), Calabar was rejected. Hence, the alternate hypothesis that there is a significant relationship between the level of awareness and practice of birth preparedness and complication readiness among couples attending antenatal clinic at University of Calabar Teaching Hospital (UCTH), Calabar was accepted in favour of pregnant women who have high awareness of birth preparedness and complication readiness.

Discussion

The findings of this study revealed that the level of awareness of birth preparedness and complication readiness among couples attending antenatal clinic at UCTH, Calabar is high. Most (73.5%) respondents have high level awareness of birth preparedness and complication readiness, while (26.5%) have low awareness. Most respondents are aware that a pregnant woman should know her expected date of delivery; labour can start before due date; a pregnant woman should make arrangement for transportation to hospital in case of emergency labour; and the danger signs such as vaginal bleeding and swelling of face and feet. The findings correspond with a previous study on assessment of birth preparedness and complication readiness among pregnant women in Orlu Local Government Area in Imo State, Nigeria. The study revealed that most of the respondents were aware of birth preparedness and complication readiness, with 80% aware of danger sings in pregnancy, and 84.8% prepared items for birth for birth such as transportation and saving money. Similarly, the findings agree with a study in south eastern Nigeria which revealed that 70.6% of the respondents were aware of the concept of birth preparedness and complication readiness. It was also revealed in this study that the level of practice of birth preparedness and complication readiness among couples attending antenatal clinic at UCTH, Calabar is high. Most (50.4%) of the respondents have high level practice, 39.1% have moderate practice, while 10.5% respondents have low practice. Most of the respondents attend antenatal care up to four times, have saved money in case of birth complications, have made arrangement for care of the home during mother's absence, and have identified and arrange for transportation to the hospital when labour begins. The result corresponds with a study which examination of the practice of birth preparedness and complication readiness among pregnant women in rural area in Chhattisgarh, India revealed that majority (73.65%) of the respondents (pregnant women) high level practice of birth preparedness. Most of the respondents have

already identified skilled birth attendant for delivery, while 52.7% of women had already identified blood donors in case of emergency. Similarly, the result corresponds with a study in Sisala East District. Ghana revealed that 58.0% of respondents attended regular antenatal clinic, saved money and made provision for transportation in case of emergency.

The findings of this study further revealed that the factors affecting birth preparedness and complication readiness among couples attending antenatal clinic at UCTH, Calabar include: distance to health facility, lack of adequate support/assistance from family members, relative and friends, lack of financial support from my husbands, lack of awareness of the components of birth preparedness and complication readiness and poor inter-personal relationship between midwives and pregnant women. When pregnant women do not receive adequate support from husbands, friends, and relatives, they may find it difficult to practice birth preparedness and complication readiness. But if they receive adequate support, it will be much easier for them to practice birth preparedness and complication readiness. Also, if pregnant women are aware of the components of birth preparedness and complication readiness, the will make sure to visit antenatal clinic at least four times, save money in case of emergency, and make provision for emergency transportation. The findings correspond with Kaiser Family Foundation (2000), who noted that most parent do not belief that teaching children about safe sex practice could protect the children, rather, it will expose them to sexual behaviour at an early stage. But if parents lack knowledge of safe sex education coupled with negative perception about the practice, providing it to the children will be difficult. This finding also agree with a facility-based cross sectional study in Migori Country, Kenya, which revealed that distance to place of delivery and lack of husband and loved ones were militating against practice of birth preparedness and complication readiness. Also, the findings agree with studies in South Eastern Nigeria and in Jimma zone, Southwest Ethiopia, which revealed that distance, husband's occupation and support, attitude of relatives were among the factors that affected birth preparedness and complication readiness.

Implication to nursing

The implication of this study to nursing is that it will create awareness and consciousness on awareness, practice and factors influencing birth preparedness and complication readiness. It will also, serve as an eye opener to health policy makers, nurse educators and nurses in general to mitigate the factors inhibiting practice of birth preparedness and complication readiness in UCTH, Calabar, Cross River State, and Nigeria as a whole. They will intensify effort target at educating pregnant women during antenatal visits and through the mass media on birth preparedness and complication readiness.

Conclusion

In conclusion, although adequate awareness and practice of birth preparedness and complication readiness is an affective of preventing maternal mortality, the extent to which it is practiced among pregnant women in some places is not as expected. This study had revealed that most pregnant women attending antenatal clinic in UCTH, Calabar have high awareness of birth preparedness and complication readiness. Although the level of practicing birth preparedness is high, but still low among some pregnant women. The factors inhibiting the practice of birth preparedness and complication readiness among couples attending antenatal clinic at UCTH, Calabar include: distance to health facility, lack of adequate support/assistance from family members, relative and friends, lack of financial support from my husbands, lack of awareness of the components of birth preparedness and complication readiness and poor inter-personal relationship between midwives and pregnant women

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Cite this article: Agba M. Awareness, practice and factors influencing birth preparedness and complication readiness among women attending antenatal clinic at University of Calabar Teaching hospital (UCTH), Calabar, Cross River state, Nigeria Int. J. Collab. Res. Intern. Med. Public Health. 2022, 14 (06), 001-004