ISSN 2187－9737 CODEN：JIZUA2 68（1）1-90（2022）

JUNTENDO MEDICAL JOURNAL

順天堂醫事雜誌

February 2022

Juntendo Medical Journal Vol. 68 No. 1 p. 1-90 Tokyo 2022. 2

68-1
(936th issue)

JUNTENDO MEDICAL JOURNAL

順天堂醫事雜誌

The History of *Juntendo Medical Journal*

This *Juntendo Medical Journal* has been published under the Japanese name *Juntendo Igaku* (順天堂医学) from 1964 to 2012. However, the origin of *Juntendo Medical Journal* dates back to the oldest medical journal in Japan, *Juntendo Iji Zasshi* (順天堂醫事雜誌), which had been published between 1875 and 1877 (total of 8 issues). Between 1885 and 1886, Juntendo issued a limited release of a research journal titled *Houkoku* [*Juntendo Iji Kenkyukai*] (報告) for a total of 39 issues.

In 1887, *Juntendo Iji Kenkyukai Houkoku* (順天堂醫事研究會報告) was published with the government's approval and we used to regard this as the first issue of *Juntendo Medical Journal*. Since then, *Juntendo Medical Journal* has undergone a series of name changes: *Juntendo Iji Kenkyukai Zasshi* (順天堂醫事研究会雜誌), *Juntendo Igaku Zasshi* (順天堂医学雑誌), and *Juntendo Igaku* (順天堂医学).

Now in commemoration of the 175th anniversary of Juntendo University, starting with the first volume issued in 2013 (Volume 59 Number 1), we return to *Juntendo Medical Journal*'s original Japanese title in 1875-*Juntendo Iji Zasshi* (順天堂醫事雜誌). We also reconsidered the numbering of the journal and set the first issue in 1875 as the initial publication of *Juntendo Medical Journal*. The Volume-Number counting system and the English name *Juntendo Medical Journal* started in 1955 from the January 10 issue. Although this is not our intension, we will retain the Volume-Number counting system to avoid confusion. However, Volume 59 Number 1 will be the 882nd issue, reflecting the sum of all issues to date: 8 issues of *Juntendo Iji Zasshi* (順天堂醫事雜誌), 39 issues of *Houkoku* [*Juntendo Iji Kenkyukai*] (報告) (47 issues combined), and 834 issues from *Juntendo Iji Kenkyukai Houkoku* (順天堂醫事研究會報告) in 1887 to the present.

出典：小川秀興（OGAWA Hideoki, M.D., Ph.D.）：順天堂醫事雜誌（Juntendo Medical Journal）2013；59：6-10.

本誌は昭和39年（1964年）から平成24年（2012年）末まで『順天堂医学』として刊行されてきた．しかし，その起源は明治8年（1875年）から10年（1877年）にかけて発刊された日本最古の医学誌『順天堂醫事雜誌』（計8巻）にある．さらに明治18年（1885年）から19年（1886年）まで，会員限定配本として順天堂醫事研究會の雑誌『報告』（計39集）が発行されている．

その後『順天堂醫事研究會報告』が明治20年（1887年）に官許を受けて公刊されたので，順天堂ではこれを通刊1号としてきた．以来，『順天堂醫事研究会雜誌』，『順天堂医学雑誌』，『順天堂医学』と名称を変更して刊行されてきた．

今般，順天堂が創立175周年を迎える平成25年（2013年）の59巻1号を期して，本来の名称である『順天堂醫事雜誌』と復刻し，その起源である明治8年（1875年）第1巻をもって創刊号（通刊第1号）とすることとした．従来の巻号と欧文誌名は，昭和30年（1955年）1月10日発行のものを1巻1号としており，欧文誌名もこれより付け始めたもので不本意であるが，混乱を避けるためにこれらを継承する．ただし，通刊数は明治8年（1875年）から19年（1886年）にかけて刊行された『順天堂醫事雜誌』8巻分と順天堂醫事研究會の雑誌『報告』39集，計47巻分を通巻834号に加え，59巻1号を通刊882号とした．

出典：小川鼎三，酒井シヅ：順天堂医学　1980；26：414-418.
小川秀興：順天堂醫事雜誌　2013；59：6-10.

Published by The Juntendo Medical Society
2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan
TEL 03-5802-1586　E-mail j-igaku@juntendo.ac.jp

20220228

Printed by Koryosha Co. Ltd.
4F, 2-31-25 Yushima, Bunkyo-ku, Tokyo 113-0034, Japan
TEL 03-3868-3352　E-mail jmj@koryo-co.com

JUNTENDO MEDICAL JOURNAL

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From the illustrator: The coronavirus infection continues to spread, and now we cannot possibly hope to enjoy traveling abroad. One day, my friend who used to love overseas trip brought me dolls made in Peru she had visited several years ago. I immediately decided to use them as a motif in my painting class. The Peruvian dolls have exotic features, being dressed in their traditional costume.

Special Reviews

Juntendo Medical Journal
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The Current Progress of Psychiatric Genomics

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Psychiatric disorders such as bipolar disorder and schizophrenia are highly heritable. While the genetic contribution to psychiatric disorders is quite sure, specific genetic factors contributing to particular conditions have long been a mystery. Empowered by the initial report of the Human Genome Project, the analysis of the comprehensive set of the human genome, called "genomics," became possible. Subsequent development of large-scale genomic technologies enabled us to elucidate various disease-related genetic information, accelerating our understanding of various diseases. Genomic research on psychiatric disorders is not an exception. In this Review, I introduce significant advancements in psychiatric genomics with a special focus on our investigation of bipolar disorder. International consortiums and advocacy groups accelerate psychiatric genomics, increasing the sample size and statistical power for robust findings. The genetic architecture of schizophrenia has been elucidated in both common and rare variant studies. The genetic architecture of autism spectrum disorder (ASD) has been elucidated mainly by rare variant analysis. As to bipolar disorder, common variant analysis precedes rare variant analysis, but we are struggling to elucidate relevant rare variants. While the genomic approach has explained specific genetic factors for particular disorders, overlapping risk genes or pleiotropy has been observed more than expected. The boundary in the current nosology of psychiatric disorders is more or less challenged. To understand the genotype-phenotype relation more deeply, an attempt to understand phenotypes based on genotypes, called the "genotype first" approach, has started. I discuss this new approach for better understanding and treatment of psychiatric disorders.

Key words: genomics, psychiatric disorder, bipolar disorder, schizophrenia, autism spectrum disorder (ASD)

Introduction: psychiatry and genetics

Psychiatric disorders such as bipolar disorder and schizophrenia are global medical problems afflicting many individuals with severe suffering. The societal cost of bipolar disorder and schizophrenia is estimated high among various medical diseases[1)]. Bipolar disorder afflicts the patients and their families with severe depression and problematic behaviors from manic episodes. Schizophrenia leads to unbearable suffering through annoying hallucinations, persecutory delusions, social withdrawal, and cognitive decline. Despite the patients' woes, we have limited choice of therapeutic strategy. The adverse effects of the medications are also problematic. Besides, the effects of psychiatric medications are serendipitously discovered, not based on our biological understanding of the mechanisms of psychiatric disorders. We need to understand the biological mechanisms of psychiatric disorders to find a new therapeutic strategy and overcome the suffering of the patients due to

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354th Triannual Meeting of the Juntendo Medical Society "Recent topics in Psychiatry" [Held on sep. 9, 2021]
[**Received Nov. 4, 2021**][Accepted Nov. 24, 2021]
J-STAGE Advance published date: Feb. 16, 2022

doi: 10.14789/jmj.JMJ21-0038-R

psychiatric symptoms.

Psychiatric disorders such as bipolar disorder and schizophrenia are highly heritable[2]. Observing that many patients have families or relatives with similar mental problems, clinicians have long noticed this fact. The high heritability of psychiatric disorders is confirmed by the diagnostic concordance rate of monozygotic twins. Monozygotic twins have the same germline genetic information. The high rate of diagnostic concordance means that the contribution of genetic factors is highly relevant to psychiatric disorders. For example, the diagnostic concordance of bipolar disorder is 40–50%[2], while the lifetime morbidity of bipolar disorder is around 1%. However, we have not fully understood the biological background of this high heritability. Specific genetic information and biological mechanisms to the onset of psychiatric disorders remain unknown.

Genetic information is coded as sequences of bases in DNA. All the creatures on Earth adopt this system. *Homo sapiens* is not an exception. After the first proposal of the double helix structure of DNA as media of genetic information, researchers have been long pursuing what specific features of DNA contribute to the phenotypes of the individual. In psychiatry, the phenotypes in the individuals correspond to the diagnosis of psychiatric disorders and their symptoms. Psychiatric researchers desire to know specific characters of DNA that contribute to psychiatric disorders. The initial effort of this endeavor started from single nucleotide polymorphisms (SNPs). SNP is one type of genetic variant as a conversion from one base to another with a frequency of one percent or more in the general population. This was a good start point because SNP is relatively easy to detect. However, the initial effort to hunt disease-related SNPs was not fruitful[3]. This effort is like fishing in the Pacific Ocean, and fishing all over the Pacific Ocean was not realistic at that time. To explore all over the Pacific Ocean, we needed a different approach.

The birth of genomic analysis

The Human Genome Project was started in 1990 by the government of the United States. This project aimed at the complete catalog of the human genome[4], which spans around three Giga base pairs as one haplotype. Empowered by the Human Genome Project and subsequent development of large-scale DNA sequencing technology such as SNP chip and next-generation sequencing[5], comprehensive human genome analysis became realistic. This new approach is called "genomics." The word "genome" means a whole set of genes, consisting of "gene" and "-ome" (a suffix meaning totality). In contrast to fishing in one spot, this approach can be compared to broad image capture by artificial space satellites. Capturing the images all over the Pacific Ocean became possible. Researchers are now armed with genomic technologies to investigate the human genome, finding a lot of variants associated with medical diseases. As the cost of genomic technologies declines, the sample size of genomic research increases, and the conclusion from the analysis becomes robust. Psychiatric genomics is not an exception.

A variant in the human genome receives different natural selection pressure with the phenotypes associated with it. Variants associated with severe diseases such as life-threatening pediatric cardiovascular diseases tend to be negatively selected, thus having a lower frequency in the general population. In contrast, variants scarcely associated with severe diseases are neutral and can have a high frequency in the general population by genetic drift. To put it the other way around, variants with higher frequency in the general population (common variants) tend to have minor effects on diseases; variants with lower frequency in the general population (rare variants) tend to have a more significant effect on diseases[6]. Figure 1 illustrates the theoretical distribution of disease-associated variants related to their effect on the disease and their frequency in the general population. Note that this illustration is a theoretical framework, and there are some exceptions to this framework, such as *APOE* and Alzheimer's disease[7, 8]. In general, the contribution of common variants is supposed to be more significant to common diseases (e.g., diabetes mellitus) than rare diseases (e.g., Mendelian diseases); the contribution of rare variants is supposed to be more significant to rare diseases than common diseases. Disease-associated common variants have been detected mainly by genome-wide association studies (GWAS) using SNP chips. SNP chips can genotype millions of SNPs simultaneously, while the investigation is limited to the pre-designed

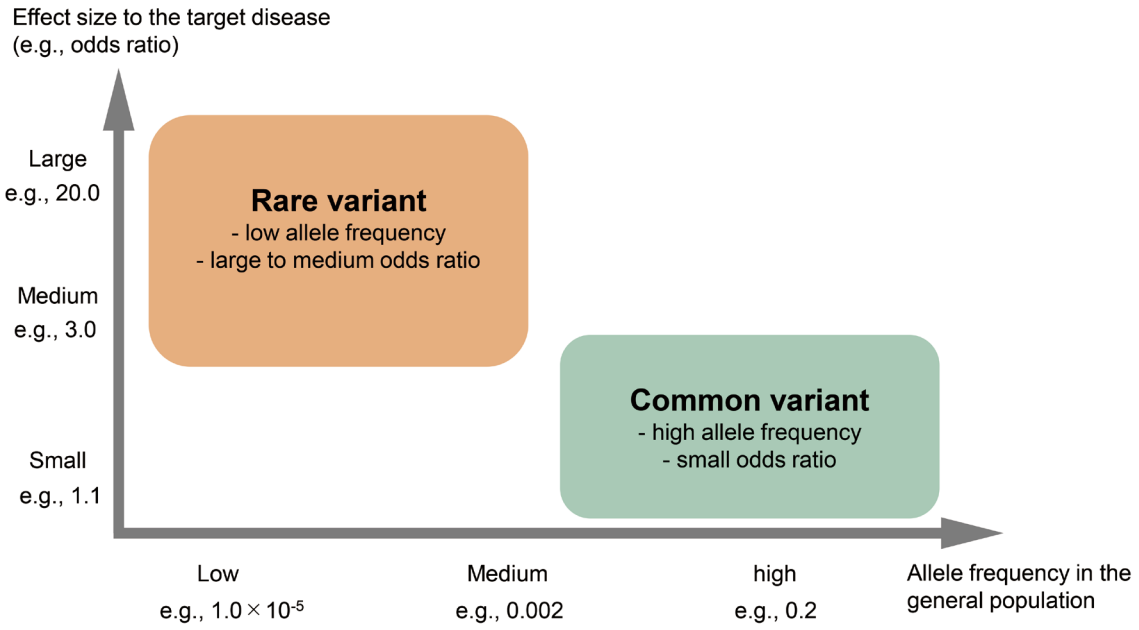

Figure 1 A schematic illustration of the disease-associated variants. The x-axis is the allele frequency in the general population, and the y-axis is the effect size to the target disease (e.g., odds ratio). Note that this illustration is a theoretical framework, and there are exceptions to this framework in reality.

SNPs. Disease-associated rare variants have been detected mainly by whole-exome sequencing using massively parallel sequencing technology (so-called next-generation sequencing). Exome sequencing can detect variants in the exonic regions (protein-coding regions), including brand-new variants yet known before, but the cost of this technology is higher than SNP chips. The technical details of these technologies are themselves interesting, but they are beyond the scope of this Review. The technical details of such genomic technologies, including newer technologies, are reviewed elsewhere[9,10].

The current psychiatric genomic investigation is advancing following this framework. We are now harvesting the fruit of the genomic analysis of psychiatric disorders to understand the biological mechanisms of psychiatric disorders[11,12]. Directly investigating the human brain is ethically and technically challenging. Biological insight from genetic studies complements this difficulty by providing indirect evidence for the etiology of psychiatric disorders. I review the major advancement of psychiatric genetics in the last decade, focusing on significant works on schizophrenia and autism spectrum disorder (ASD), and our investigation on bipolar disorder.

Schizophrenia

Schizophrenia is a severe psychiatric disorder characterized by auditory hallucinations and persecutory delusions. Schizophrenia afflicts around one percent of the general population, afflicting the patients with painful experiences and social dysfunction due to cognitive decline. Schizophrenia is regarded as one of the major global medical issues because the societal cost of schizophrenia is high among other medical diseases[1]. Schizophrenia has long been the most major disease concept in psychiatry and is also intensively investigated in genomic research. The prevalence of around one percent is on the threshold of common or rare diseases. Thus, genomic investigation of schizophrenia is advancing under two models: research to common variants as common diseases and rare variants as rare diseases.

Several hundred common variants associated with schizophrenia have been elucidated from the GWASs of international collaboration using SNP chips[13-16]. Psychiatric Genomics Consortium (PGC) is the most influential international collaboration of psychiatric genomics[17], reporting several significant results[13-15]. Precisely speaking, the associated common variants are not always the direct cause of the association but represent the genomic loci

around them. We need to be cautious in interpreting the "associated genes" in these studies. The newest study of PGC (PGC3) consists of around 70,000 cases with schizophrenia and 240,000 controls, revealing 270 loci associated with schizophrenia[18]. The effect size of each variant (or each genomic locus) is relatively small, with an odds ratio of 1.3 at most[18, 19], but the number of the association is biologically informative. The associated genes or loci are enriched in the gene sets related to synapse, especially those coding postsynaptic structure proteins. From the viewpoint of genetic studies of common variants, schizophrenia is a disease of synaptic dysfunction. Notably, the associated genes include *DRD2*, coding a subunit of dopaminergic receptors in the postsynaptic structure. One of the most promising hypotheses for the etiology of schizophrenia has been the dysregulation of the dopaminergic system[20]. The studies of common variants support this long-held hypothesis in psychiatry.

Following the promising results of studies of common variants, schizophrenia-associated rare variants have been elucidated[21-28]. The current understanding of rare variants for schizophrenia is mainly derived from studies using whole-exome sequencing. A meta-analytic effort from Broad institute aggregates an enormous volume of exome sequencing data of 24,000 cases and 97,000 controls from all over the world[29]. Nine genes are robustly associated with schizophrenia through deleterious mutations in these genes: *SETD1A*, *CUL1*, *XPO7*, *TRIO*, *CANCA1G*, *SP4*, *GRIA3*, *GRIN2A*, and *HERC1*. The deleterious mutations are mainly protein-truncating mutations such as nonsense or frameshift mutations. These mutations tend to be depleted or extremely rare in the general population, thus are ultra-rare variants. Notably, *SP4* and *GRIN2A* are deeply associated with schizophrenia through rare and common variants[18, 29]. *GRIN2A* codes a subunit of NMDA receptors, one of the key components of glutamatergic neurotransmission. Another gene coding a key component of glutamatergic neurotransmission (AMPA receptor), *GRIA3*, is also robustly associated with schizophrenia through rare variant analysis[29]. Dysfunction of glutamatergic neurotransmission is one of the most promising hypotheses for the etiology of schizophrenia[30, 31]. The studies of both common and rare variants support this notion.

Autism spectrum disorder (ASD)

ASD is a major neurodevelopmental disorder characterized by difficulties in social interaction/communication and restricted/repetitive behavior. This disease concept is highly spectrum, and the boundary between affected and unaffected status is difficult to define. Studies of rare variants mainly drive the genetics of ASD. While the number of ASD-associated common variants is few[32], the number of ASD-associated genes with rare variants is culminating. Exploration of rare variants in ASD is highly powered by studies on sporadic trios with ASD to investigate de novo mutations[33-40]. De novo mutation is a newly arising mutation in the parents' gametogenesis, detected as germline variants in the probands while not as germline variants in the parents. De novo mutation is a promising candidate to explain sporadic cases in which only the proband has the target disease (ASD), and the parents have no target disease.

Accumulating evidence has been elucidating the genes hit by de novo mutations (mainly protein-truncating mutations) robustly associated with ASD, including *CHD8*, *SCN2A*, and *ARID1B*, to name a few. The most extensive study of de novo mutations in ASD to date analyzed over 6,000 families with ASD and detected 102 genes as promising candidate genes for ASD[40]. Simons Foundation Autism Research Initiative (SFARI) is aggregating and curating the genetic research results on ASD so far, listing several hundreds of candidate genes for ASD in a user-friendly website: https://gene.sfari.org/. Around 200 genes are listed as robustly associated with ASD in this curation. Advocacy groups such as SFARI are influential players as a funding agency and promoting agency for the general public in advancing genetic studies on ASD[41]. Thanks to the effort of advocacy groups, rare variant studies on ASD are more advanced than studies on other disorders, exemplifying a research paradigm for studies on other disorders.

Bipolar disorder

Bipolar disorder is a severe psychiatric disorder characterized by mood swings of depression and manic states. Bipolar disorder is relatively common, affecting around 1% of the population. Suffering

from severe depression and problematic behavior from manic moods significantly impact patients' social life. Elucidating the pathophysiology of bipolar disorder and the development of new treatments are required[42]. Similar to the situation of schizophrenia, the prevalence of around 1% is on the threshold of common or rare diseases. Genomic investigation of bipolar disorder is also advancing under the two models: research to common variants as common diseases and rare variants as rare diseases.

Studies on common variants precede studies on rare variants in the genetics of bipolar disorder[43–46]. GWASs on bipolar disorder have detected 64 loci associated with bipolar disorder using a consortium-based approach with aggregated 42,000 cases and 370,000 controls[44]. As with the situation in schizophrenia, the effect size of each variant is relatively small. The odds ratio of the associated loci in bipolar is 1.15 at most, which is even smaller than schizophrenia. However, the number of the association is biologically informative, elucidating the gene sets related to synapse and ion channels. Synaptic structure and function are relevant to both bipolar disorder and schizophrenia. The phenotypes of bipolar disorder and schizophrenia are apparently different, but the correlation of associated common variants is notable between bipolar disorder and schizophrenia with a genetic correlation of around 0.68[44, 47–49]. This high correlation is probably against most clinical psychiatrists' intuition and should be the focus of future psychiatric genomics[50].

In contrast to studies on common variants, studies on rare variants in bipolar disorder lags behind in sample size despite several pioneering studies[51–55]. Therefore, we are investigating rare variants, especially de novo mutations, to elucidate the genetic architecture of bipolar disorder[53, 56]. De novo mutations are subject to little natural selection and are thought to contain disease-associated mutations with significant effects. In particular, we are investigating extremely rare de novo mutations not found in the general population to find potential disease-associated rare variants[56]. We also investigated postzygotic de novo mutations (mosaic or somatic mutations) in addition to classical de novo mutations (i.e., germline de novo mutations) to explore the unknown genetic architecture of bipolar disorder (Figure 2). While several studies have reported on mosaic mutations in ASD[57–60], pathological roles of mosaic mutations

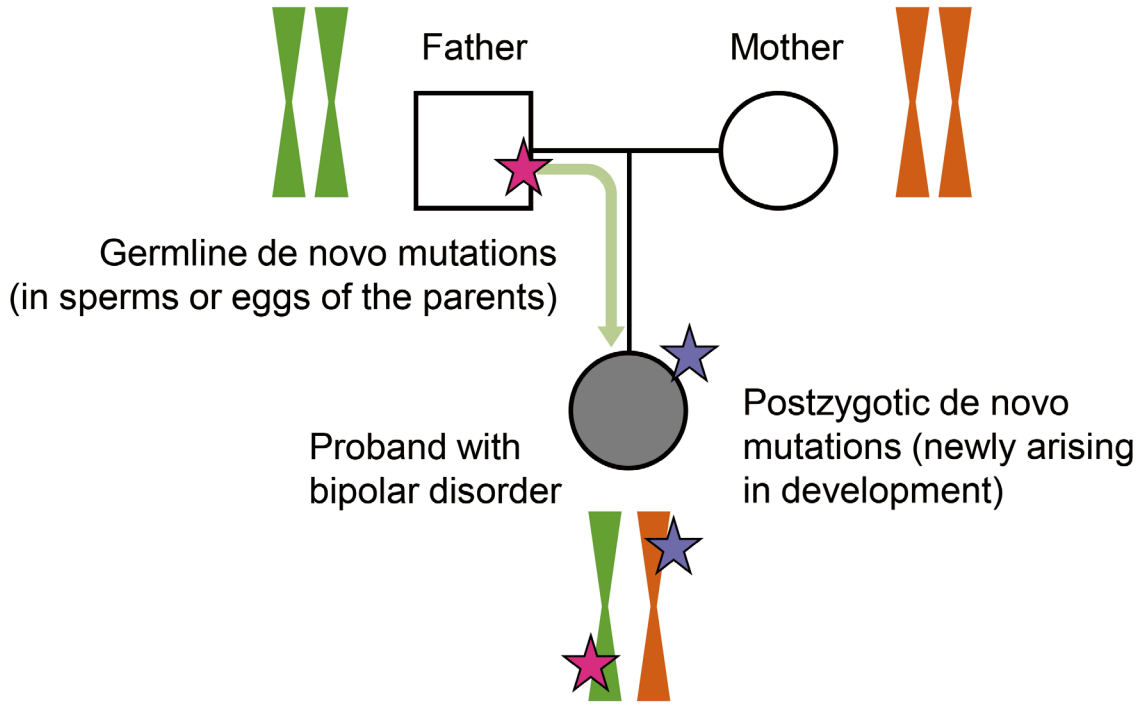

Figure 2 A schematic illustration of the two classes of de novo mutations: germline and postzygotic de novo mutations. The germline de novo mutations arise in the gametogenesis of the parents. The postzygotic de novo mutations arise in the developmental process of the proband after the fertilization.

for psychiatric disorders remained known. Participants in our study were recruited through Bipolar Disorder Research Network Japan (BDRNJ, http://bipolar.umin.jp/), a network of patients, families, and researchers across Japan. Thanks to BDRNJ, we could report de novo mutation analysis with 354 families with bipolar disorder[56]. This number is the world's largest number for de novo mutation analysis in bipolar disorder to date. Research networks consisting of the patients and researchers such as BDRNJ are influential players in current genomic research.

Among the extremely rare de novo mutations in bipolar disorder, protein-truncating (loss-of-function) de novo mutation in a high probability of loss-of-function intolerance (pLI) genes is significantly more observed in bipolar disorder than in control. High pLI genes are the genes in which loss-of-function mutation is less observed in the general population than the theoretical estimation, meaning its susceptibility to natural selection by loss-of-function. This result is naturally expected for severe psychiatric disorders and is a common observation with schizophrenia and ASD[24, 40, 61]. Among the extremely rare de novo mutations, deleterious mutations are enriched in the genes related to synapse and calcium ions. This result is consistent with the results of common variants and other biological studies on bipolar disorder[42, 62, 63], supporting the dysregulation of synapse and calcium signaling as the promising candidate mechanisms of bipolar disorder.

Among the genes hit by deleterious mutations found in this study, *KMT2C* is known to cause a severe neurodevelopmental disorder (Kleefstra syndrome[64]) much more severe than bipolar disorder. We investigated the detail of the mutation in *KMT2C* to explain the apparent phenotypic difference between bipolar disorder and Kleefstra syndrome. Surprisingly, the mutation is, in fact, a mosaic mutation (postzygotic de novo mutation) in the proband's body. The mutation exists only in some cells and should have occurred in the process of early development. Encouraged by this finding, we investigated postzygotic de novo mutations in patients with bipolar disorder. Among the postzygotic de novo mutations in bipolar disorder, deleterious mutations are enriched in the genes known to cause neurodevelopmental disorders (e.g., *KMT2C*). In addition, we found two deleterious mutations in *SRCAP* in two independent patients with bipolar disorder. *SRCAP* is known to cause a severe neurodevelopmental disorder, Floating-Harbor syndrome[65]. This result leads to an interesting hypothesis: mosaic mutations in neurodevelopmental disorder genes cause milder phenotypes, including bipolar disorder. If this hypothesis holds true, bipolar disorder shares pathological mechanisms with severe neurodevelopmental disorders. Encouraged by rare variant studies on developmental disorders to understand the pathological mechanisms of psychiatric disorders[66], we are now proceeding with mosaic mutation analysis to confirm this hypothesis[67].

We conducted a comprehensive study of two types of mutations, germline and postzygotic (mosaic) de novo mutations, and elucidated a part of the genetic architecture of bipolar disorder[56]. However, analysis with more families and patients with bipolar disorder is necessary to obtain more reliable and more profound knowledge. Future genomic research will be more empowered by research networks consisting of the patients and researchers such as BDRNJ. Through such collaboration, we will understand the pathological mechanisms and develop a new therapeutic/preventive strategy for bipolar disorder.

Future direction: genotype first approach in psychiatry

In this Review, I have overviewed the current understanding of major psychiatric disorders by genomic investigation. Genomic analysis is one of the most powerful approaches to elucidate the biological mechanisms of psychiatric disorders. However, accumulated data from genomic studies so far proposes a critical question to the current diagnostic boundary among psychiatric disorders. Some genes are simultaneously associated with different disorders through common and rare variants[47-49]. This is particularly notable for common variants associated with bipolar disorder and schizophrenia. In addition to the shared risk of common variants, *AKAP11*, the first gene reported to be associated with bipolar disorder through a gigantic meta-analysis of exome sequencing for rare variants, is also associated with schizophrenia[68]. These results suggest that major psychi-

atric disorders share common pathological mechanisms, and prompt us to rethink the current disease concepts in psychiatry.

Researchers have started a new approach, the "genotype-first approach," to resolve this issue [69-73]. The genotype-first approach is a research strategy to associate a specific genotype to a broad range of clinical phenotypes, not limited to conventional psychiatric symptoms but including somatic and physiological signs[74, 75]. Traditional genetic research has adopted the opposite approach, the "phenotype-first approach," which is a research strategy to associate a specific phenotype to genotypes. The genotype-first approach is essentially free from the current nosology of psychiatric disorders. This approach has begun to characterize the individuals with the established risk variants significantly affecting the onset of psychiatric disorders[76-80]. Starting from the traditional diagnosis and genomic analysis, the researchers characterize the individuals with extensive medical evaluations including physical and physiological examinations to explore the genotype-phenotype correlation (Figure 3). The question is how much the genotype-first approach effectively characterizes possible disease concepts in a wide range of psychiatric disorders. Some clinicians have begun to feedback genetic information of such risk variants to the patients regardless of conventional psychiatric diagnosis[81]. This approach will benefit future psychiatric research, but the answer will be evident through our effort with this genotype-first approach.

Acknowledgements

I thank all the members of the Department of Psychiatry, Faculty of Medicine, Juntendo University, for valuable discussion and clinical insight for this review.

Funding

This work was partly supported by AMED under Grant Number JP20dm0307028 (Strategic International Brain Science Research Promotion Program [Brain/MINDS Beyond] for M.N.), and

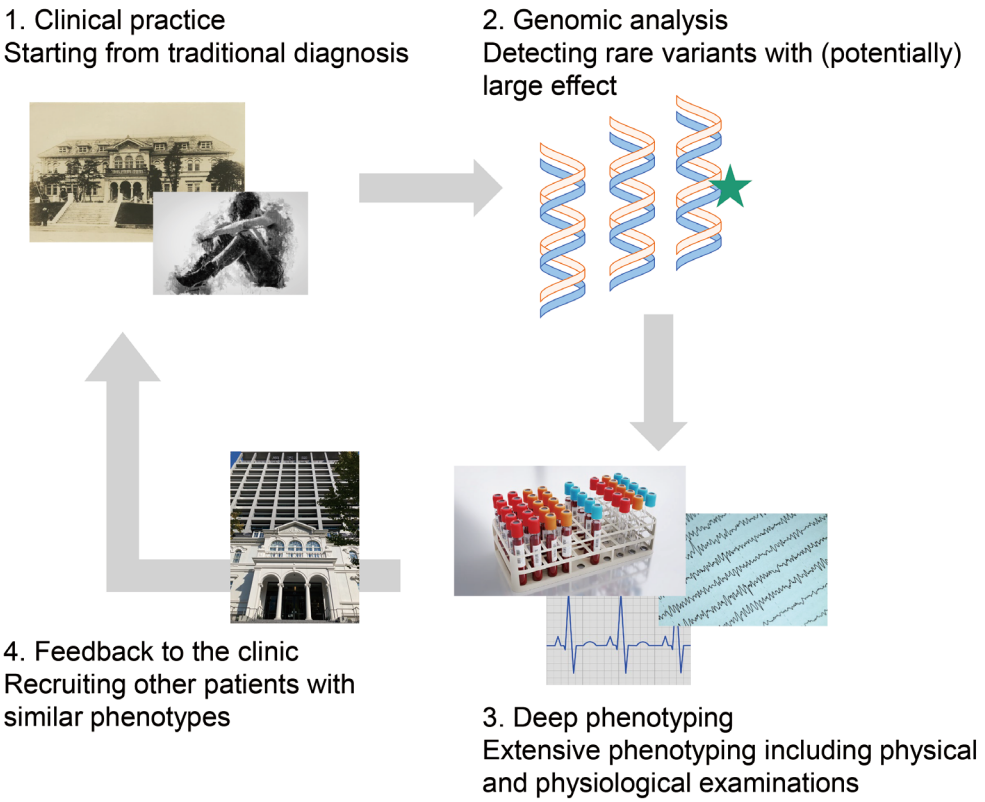

Figure 3 A schematic illustration of the genotype-first approach in our department (Department of Psychiatry, Faculty of Medicine, Juntendo University). The copyright-free images of clinical tests are derived from Pixabay (https://pixabay.com/). The historical image of the Juntendo clinic is derived with permission from Gakko-hojin Juntendo.

JSPS KAKENHI under Grant Number JP18K15479 (M.N.), JP16H06277 (M.N.).

Author Contributions

M.N. wrote and checked the manuscript.

Conflict of interest statements

M.N. belongs to the Department of Molecular Pathology of Mood Disorders, Faculty of Medicine, Juntendo University, a joint laboratory of Juntendo University and Sumitomo Dainippon Pharma.

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Special Reviews

Juntendo Medical Journal
2022. 68(1), 12–16

Prevention of Delirium Via Melatonin and Orexin Neurotransmission

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The fundamental conception of delirium is altered arousal. In addition, sleep–wake cycle disturbances including insomnia, excessive daytime napping, and disintegration of the expected circadian patterns have been described as a characteristic component of delirium for decades, and demonstrated to be a core symptom domain of delirium. Although non–pharmacological interventions are successful to some extent, they have limitations due to various biological etiologies for delirium. Among pharmacological interventions, antipsychotics seem to be effective, but they are not suitable for preventive use because of relatively frequent side–effects such as extrapyramidal symptoms. Recently, new type of drugs for insomnia have been focused with respect to delirium prevention. Recent meta–analyses show effectiveness of melatonin receptor agonists and orexin receptor antagonists for delirium prevention, and real–world data support them.

Key words: delirium, melatonin, orexin, prevention, sleep–wake cycle disturbance

1. Introduction

The fundamental conception of delirium is altered arousal[1]. In addition, sleep–wake cycle disturbances including insomnia, excessive daytime napping, and disintegration of the expected circadian patterns have been described as a characteristic component of delirium for decades, and demonstrated to be a core symptom domain of delirium[2]. Although non–pharmacological interventions are successful to some extent[3], they have limitations due to various biological etiologies for delirium. Among pharmacological interventions, antipsychotics seem to be effective, but they are not suitable for preventive use because of relatively frequent side–effects such as extrapyramidal symptoms. Recently, new type of drugs for insomnia have been focused with respect to delirium prevention.

2. Melatonin receptor agonists for delirium prevention

Melatonin, a pineal gland hormone, regulates the sleep–wake cycle, and there is some emerging literature suggesting that melatonin prophylaxis may reduce delirium incidence or a long–lasting episode of delirium[4–6]. Sultan reported that after medications were given orally 90 min before operative time and at sleep time at night of operation, the melatonin group showed a statistically significant decrease in the percentage of postoperative delirium to 9.43% (5/53 patients), compared with the control group (32.65% [16/49], relative risk 0.29, P = .0062)[4]. Al–Aama et al. reported that melatonin (0.5 mg every night for 14 days or until discharge) was associated with a lower risk of delirium (12.0% vs. 31.0% [placebo], P = .014), with an odds ratio (OR), adjusted for dementia and co–morbidities of 0.19[5]. de Jonghe et al. reported

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354th Triannual Meeting of the Juntendo Medical Society "Recent topics in Psychiatry" [Held on sep. 9, 2021]
[**Received Nov. 3, 2021**][Accepted Nov. 10, 2021]
J–STAGE Advance published date: Feb. 4, 2022

doi: 10.14789/jmj.JMJ21–0035–R

that despite no effect of melatonin (3 mg in the evening for 5 consecutive days) on the incidence of delirium (29.6% [55/186 patients scheduled for acute hip surgery] for the melatonin group vs. 25.5% [49/192] for the placebo group), a smaller proportion of patients in the melatonin group than in the placebo group experienced a long-lasting episode of delirium (> 2 days) (25.5% v. 46.9%; P = .02)[6].

Along the similar conception, we examined whether ramelteon, a melatonin agonist with 6- and 3-fold higher affinities for melatonin 1 (MT_1) and melatonin 2 (MT_2) receptors, respectively, compared to those of melatonin, is effective for the prevention of delirium in a multi-center, rater-blinded, randomized placebo-controlled clinical trial[7]. Eligible patients were 65-89 years old, newly admitted to intensive care units and regular acute wards in four university hospitals and one general hospital due to emergency, and able to take medicine orally. Patients were excluded from the study if they had an expected stay or life expectancy less than 48 h. Sixty-seven patients were randomly assigned using the sealed envelope method to receive ramelteon (8 mg/day; n=33) and placebo (n=34) every night for 7 days, and the main outcome measure was incidence of delirium as determined by the DSM-IV-TR. Ramelteon was associated with lower risk of delirium (3% vs. 32%, P =.003), with a relative risk of 0.09 (95% confidence interval [CI], 0.01-0.69). Even after controlling for risk factors such as age, diagnosis of dementia, and admission diagnosis of infection, ramelteon was still associated with a lower incidence of delirium (P =.01; odds ratio, 0.07; 95%CI, 0.008-0.54). Kaplan-Meier estimates of time to development of delirium were 6.94 days (95%CI, 6.82-7.06 days) for ramelteon and 5.74 days (5.05-6.42 days) for placebo. Comparison by log-rank test showed that the frequency of developing delirium was significantly lower in patients taking ramelteon than in those taking placebo (χ^2=9.83, P =.002). Furthermore, ramelteon was associated with lower risk of delirium among patients with the Clinical Dementia Rating (CDR) ≥0.5 (the ramelteon group, 6% vs. the placebo group, 62%, P =.003), with a relative risk of 0.15 (95% CI, 0.02-0.96)[8]. Thus, these findings suggest that ramelteon administered nightly to elderly patients admitted for acute care provides protection against delirium, and support a possible pathogenic role of melatonin neurotransmission in delirium. One limitation in clinical practice, especially in an intensive care situation, is the lack of intravenous formulations of melatonin and its agonists.

Another possibility of mechanism for preventive effects of melatonin and ramelteon on delirium other than improvement in sleep-wake cycle is anti-microbial properties. Fink et al. reported that survival rate in rats experimentally having developed sepsis was significantly improved after administration of ramelteon or melatonin 1.0 mg/kg, compared with vehicle-treated animals, and that coadministration of melatonin receptor-antagonist luzindole abolished this effect completely[9]. As infection is a clinical factor that might precipitate delirium[10], anti-septic effects of melatonin and ramelteon might be associated with the preventive effects on delirium. This finding can be partially explained through change in the balance between two pathways of tryptophan metabolism under inflammation. Tryptophan is metabolized through two major pathways, the kynurenine pathway and the methoxyindole pathway. The methoxyindole pathway generates serotonin, which is a further substrate for melatonin biosynthesis. The kynurenine pathway can be activated as a result of inflammatory stimuli[11]. This change in the balance between two pathways of tryptophan metabolism can decrease in melatonin biosynthesis. Therefore, administration of melatonin or ramelteon under systemic inflammation, which may cause delirium, can compensate for lack of melatonin, resulting in the prevention of delirium.

Recent meta-analysis shows effectiveness of melatonin receptor agonists for delirium prevention[12].

3. Orexin receptor antagonists for delirium prevention

Orexin is an alerting neuropeptide produced by neurons located predominantly in lateral hypothalamic area, perifornical area and posterior hypothalamus[13]. The orexin-A levels in cerebrospinal fluid (CSF) during active wake state are highest during the dark phase in nocturnal rodents and highest during the light phase in diurnal species[14]. As a primary arousal signal in wake control, orexin

signaling is necessary for normal circadian regulation of consolidated wakefulness. Accordingly, as compared to melatonin, orexin is predominantly secreted during daytime in humans[13]. In contrast to melatonin, it has been reported that orexin secretion decreases by 10% only in older adults as compared to younger adults[15].

Interestingly, as compared to controls, patients with moderate to severe Alzheimer disease were shown to have higher mean orexin levels in CSF. Additionally, these patients had significantly impaired nocturnal sleep compared to controls and patients with mild Alzheimer's disease[16]. Furthermore, significantly higher levels of orexin in the brain of rats with acute pancreatitis were reportedly found when compared to healthy controls[17]. As dementia and inflammation are risk factors for delirium, it is possible that patients with delirium have increased orexin levels, thus accounting for the resultant sleep-wake disturbance[18].

Suvorexant, a potent and highly selective for orexin-1 receptor and orexin-2 receptor antagonist receptor antagonist, is an FDA approved treatment for primary insomnia in U.S. Suvorexant has been associated with improvements in subjective measures of total sleep time (sTST), time to sleep onset (sTSO), and wake after sleep onset (sWASO)[19], without altering NREM and REM sleep architecture as assessed by electroencephalographic monitoring[20]. The scientific rationale for using suvorexant for delirium prevention was that such character of suvorexant promoting natural sleep could improve sleep-wake cycle disturbance in delirium. High selectivity for orexin-1 and orexin-2 receptor antagonism[21] and little affinity for acetylcholine receptors (Ki>10μM)[22] may be advantage for delirium prevention. Reportedly, another dual orexin receptor antagonist did not lower hippocampal acetylcholine[23]. Thus, we hypothesized that suvorexant would have effects of preventing delirium.

To assess the efficacy of suvorexant in prevention of delirium, our group conducted a multicenter, rater-blinded, placebo-controlled RCT in ICUs and acute-phase wards. Eligible patients were aged 65-89 years, who were newly admitted due to medical and surgical emergency, able to take medicine orally, and expected to stay less than 48 hours. Study participants were randomly assigned to suvorexant (15 mg/day) (n=36) or placebo (n=36) nightly for 3 days. Main outcome measure was incidence of delirium according to the DSM-5. Patients taking suvorexant developed delirium less frequently than those taking placebo (suvorexant, 0% (n/N = 0/36) vs. placebo, 17% (6/36), P=0.025)[24]. With respect to changes in sleep-wake cycle disturbance score (item #1) of DRS-R-98, analysis of variance (ANOVA) revealed a tendency for main effect of treatment, suggesting the potential of suvorexant to improve sleep-wake cycle disturbance that is a core feature of delirium.

Another RCT examining the effects suvorexant on delirium prevention in ICU setting showed that, as compared to placebo, suvorexant led to significant reduction in incidence of both clinical delirium (14.7% vs. 33.3%, P=0.069) and sub-syndromal delirium symptoms (17.6% vs. 47.2%, P=0.011)[25]. Furthermore, Kaplan-Meier estimates revealed that time to delirium onset was significantly longer in the suvorexant group as compared to the placebo group. These findings, taken together, suggest that suvorexant, a potent and selective orexin antagonist, has beneficial effects on delirium prevention, and highlight the importance of correcting sleep-wake cycle disturbance in prevention of delirium.

Recent meta-analysis shows effectiveness of orexin receptor antagonists for delirium prevention[26].

4. Real-world effectiveness of melatonin receptor agonists and orexin receptor antagonists for delirium prevention

After success of RCTs on delirium prevention by ramelteon and suvorexant, we choose these drugs for patients who have risk factors for delirium in clinical practice. So, we examined whether ramelteon and/or suvorexant would affect delirium prevention among both patients at risk for but without delirium (patients-at-risk), and those with delirium (patients-with-delirium) on the night before a consultation. This multicenter, prospective, observational study was conducted by trained psychiatrists as consultation-liaison psychiatric services between October 2017 and October 2018. Patients who were age 65 years or older and hospitalized because of acute diseases or elective surgery, had risk factors for delirium, and had insomnia or delirium on the night before the consultation were prescribed ramelteon and/or suvorexant. The decision to take medication was left to the

discretion of each patient. The primary outcome was incidence of delirium based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, during the first 7 days. Among 526 patients-at-risk, those taking ramelteon and/or suvorexant developed delirium significantly less frequently than those who did not, after controlling for the effects of risk factors on the estimate of an independent association between the effects of ramelteon and/or suvorexant and the outcome of developing delirium (15.7% vs. 24.0%; odds ratio [OR]: 0.48, 95% confidence interval [CI]: 0.29–0.80, P = 0.005)[27]. Similar results were found among 422 patients-with-delirium (39.9% vs. 66.3%; OR: 0.36, 95%CI: 0.22–0.59; P < 0.0001). Thus, ramelteon and suvorexant appears to be effective for delirium prevention in real-world practice.

5. Conclusion

According to the evidence, we choose ramelteon first, and orexin receptor antagonists second for insomnia in elderly patients to prevent developing delirium. Thus, a potent melatonin agonist ramelteon and orexin receptor antagonists play important roles not only in insomnia but also in the prevention of delirium.

Acknowledgments

Not applicable.

Funding

This work was supported by the JSPS KAKENHI Grant Number 20K07927. The sponsor of the study had no role in the study design, data collection, data analysis, data interpretation, writing of the report, or decision to submit the paper for publication.

Author contributions

Kotaro Hatta designed the study, obtained funding, analyzed the data, interpreted the data, drafted the report, and contributed to and have approved the final manuscript.

Conflicts of interest statement

Dr Hatta has received lecture honoraria for Dainippon-Sumitomo, Eisai, Janssen, Meiji Seika, MSD, and Otsuka.

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Special Reviews

Juntendo Medical Journal
2022. 68(1), 17–24

Bipolar Disorder: From Pathophysiology to Treatment

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Bipolar disorder is a mental disorder that involves a manic or hypomanic state and a depressive state, and was once called manic–depressive disorder and was considered one of the two major mental disorders along with schizophrenia. Major depressive disorder, on the other hand, is a disorder in which only depressive states occur, and the two are sometimes referred to together as "mood disorders. This review will introduce the pathophysiology, diagnosis, epidemiology, and treatment of bipolar disorder, focusing on the current situation in Japan.

Key words: depression, mania, lithium, mood stabilizers, anticonvulsants

Introduction

Bipolar disorder is a psychiatric disorder characterized by recurrent manic or hypomanic and depressive states, and was formerly called "manic–depressive illness" and was considered one of two major psychiatric disorders along with schizophrenia. Major depressive disorder is a disorder in which only the depressed state occurs. The two are sometimes referred to together as "mood disorders", though DSM–5 discarded this category because bipolar disorder also shares some features with schizophrenia. One manic episode is sufficient for the diagnosis of bipolar I disorder, whereas at least one hypomanic episode and one major depressive episode are necessary for the diagnosis of bipolar II disorder.

In this review, pathophysiology, diagnosis, epidemiology and treatment of bipolar disorder are summarized, and the current situation in Japan is also introduced.

Symptoms

Bipolar disorder is characterized by two contrasting mental states, that is, manic or hypomanic episodes and depressive episodes. Between these episodes, patients experience euthymic, remission states.

Manic state

In the manic state of bipolar I disorder, a patient moves around without sleeping and continues to talk without rest, and because of this, the family is exhausted. While being active, the patient cannot focus on one thing and cannot work efficiently. In addition, it is common for a manic patient to make expensive purchases, make large amounts of debt, or cause legal problems. In many cases, they lose their social credibility by making unreasonable efforts that are likely to fail. It may develop into a grandiose delusion such as having supernatural powers.

In a manic state, the patient is often unaware of his or her changes and feels refreshed and in better shape than usual, so even if he or she is having

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354th Triannual Meeting of the Juntendo Medical Society "Recent topics in Psychiatry" 〔Held on sep. 9, 2021〕
〔**Received Sep. 10, 2021**〕〔Accepted Oct. 11, 2021〕
J–STAGE Advance published date: Dec. 17, 2021

doi: 10.14789/jmj.JMJ21–0026–R

trouble, often the patient does not have an awareness that he or she is in trouble or annoys others.

Hypomanic state

On the other hand, in the hypomanic state of bipolar II disorder, the patient is energetic as if he or she has changed from the usual, becomes active in human relations, moves around without hesitation even after a short period of sleep, and looks clearly "high" to those around him or her compared to the usual. However, they do not cause trouble to the people around them as in a manic state.

Depressive state

While the manic state is the most troubling symptom for the family, the depressive state is the most painful for the patient. The two core symptoms of depression are "depressed mood," which is a feeling of inexpressible annoyance that lasts all day, every day, and "loss of interest and pleasure," which is a loss of interest in everything and the inability to feel happy or joyful in anything. The presence of at least one of these two symptoms is considered necessary for diagnosis.

Including these two essential symptoms, depression is defined as the daily occurrence of five or more of the various symptoms of depression for two weeks or more, such as sleep disturbance, decreased or increased appetite (and weight loss or gain), fatigue, psychomotor retardation (slowing down of movements), guilty feeling, loss of concentration, and suicidal thoughts.

Clinical course

In bipolar disorder, there is often an interval of about five years between the first episode (depression or mania) and the next. During the remission state, when mania and depression have subsided, there are no symptoms, but if preventive therapy is not used, relapse will occur in most cases. If left untreated, the inter-episode interval gradually shortens over time[1], and if the disease shifts to rapid cycling (four or more episodes per year), it becomes difficult to respond to pharmacotherapy.

Comparing the duration of the manic state and depressive state, the duration of the depressive state is longer, and the patient is often unaware of the manic or hypomanic state, so many patients visit the clinic in a depressed state. However, in many cases, patients do not tell their doctors about their previous manic or hypomanic states at the time of their visit, in which case they are diagnosed with major depressive disorder and do not receive appropriate treatment.

Bipolar disorder is a serious illness that can be life-threatening in its depressive state due to suicide and socially life-threatening in its manic state due to the consequences of its behavior. On the other hand, bipolar patients are also known to be at increased risk for cardiovascular disease, and cardiovascular disease is the leading cause of death in bipolar patients[2].

Epidemiology

Worldwide, bipolar I disorder is considered to affect around 1% of the population, and 2–3% if both bipolar I and II are included[1].

On the other hand, in Japan, epidemiological studies large enough to estimate the prevalence have not been conducted, and the lifetime prevalence of bipolar I and II patients combined is reported to be about 0.16 to 0.6%[3–5], which is lower than in Europe and the United States. In the United States, the prevalence of bipolar disorder is lower in Asians compared with other ethnicities, suggesting that different genetic backgrounds may underlie this difference[5].

It is reported that 16% of patients who are being treated for the depressive state are bipolar disorder[6], which is a higher percentage than the difference in lifetime prevalence (lifetime prevalence of depression is about 15% worldwide and about 7% in Japan). This may be because, unlike depression, in which about a half of the patients experience only a single episode for a lifetime, bipolar disorder is characterized by multiple recurrent manic and depressive episodes.

Diagnosis

Bipolar disorder is classified into two categories based on the degree of mood elevation. The manic state is so severe that it interferes with family and work and requires hospitalization; On the other hand, the hypomanic state is a state of mood elevation in which the person is clearly different from the person as usual but is not so severe to require hospitalization.

Bipolar disorder with a manic state is called

bipolar I disorder. Even in cases where the only manic state is observed, a depressive state often appears in the course of the disease, and the diagnosis of bipolar I disorder is made even when no depressive state is seen[7].

On the other hand, bipolar disorder with both hypomanic state and depressive state is called bipolar II disorder.

If left untreated, bipolar I disorder can lead to multiple cycles of manic and depressive states, during which the foundation of one's life, such as relationships, social trust, work and family, is greatly damaged. However, treatment and coping strategies for bipolar disorder have been formulated, and in many cases, it is possible to control the illness and lead a social life.

When a depressive patient visits a clinic, the criteria for a depressive episode are checked after ruling out depression due to general medical diseases or depression due to substances or drugs. In addition, the presence or absence of a history of manic or hypomanic states should be checked. To diagnose major depressive disorder, it is necessary to confirm the absence of a history of manic or hypomanic states. However, it is not easy to accurately diagnose past hypomania, and the diagnosis of bipolar II disorder, in particular, tends to vary among doctors[8]. The depressive state of bipolar disorder is characterized by a family history of bipolar disorder, young age of onset (less than 25 years old), and psychotic symptoms (e.g., auditory hallucinations, delusions)[9], but these alone cannot be used to diagnose bipolar disorder, and there is still no test that can help differentiate between the two. In Japan, near-infrared spectroscopy (optical topography) is covered by insurance as an aid in the differential diagnosis of depression, but there is little evidence that this method is actually useful for differential diagnosis, and worldwide, this method is not considered to be useful for differentiating depression from bipolar disorder[10]. Although many other biomarkers for differentiating depression and bipolar disorder have been studied, none have been confirmed in multiple studies and have established diagnostic significance[11].

Both manic and depressive states may present with psychotic states such as delusions, auditory hallucinations, or catatonic states such as stupor.

When manic states first appear, it may be difficult to distinguish them from schizophrenia if psychotic symptoms are in the foreground. In addition, patients who initially present with a short-term psychotic disorder may subsequently develop bipolar disorder.

Treatment

Treatment goals

In the treatment of the major depressive disorder, the goal is to cure the depressive state, and in most cases, the treatment is terminated after about one year of recovery. On the other hand, in the case of bipolar disorder, the manic and depressive states will eventually be cured even if left untreated, but the manic and depressive states recur in most cases, so the goal of treatment is to prevent these episodes, and the key to treatment is how to prevent the manic and depressive states after they are cured. If treatment is stopped after the manic state is ameliorated, relapse will occur repeatedly, resulting in significant social damage and may also cause cognitive dysfunction[12].

It is not easy to continue medication for a lifetime in a state of remission when symptoms have subsided, and a combination of pharmacotherapy and psychosocial intervention that promotes acceptance of the disease is necessary. Patients go through various stages before accepting the disease, such as doubting the doctor's diagnosis, doctor shopping searching for another, better diagnosis, self-stigma, and anxiety about relapse. Therefore, it is important to monitor how the patient perceives the disease and to provide psychotherapeutic treatment according to the stage of the disease.

Pharmacotherapy

Medications other than antipsychotics used in the treatment of bipolar disorder are called mood stabilizers. The mood stabilizers used in Japan include lithium and three antiepileptic drugs: lamotrigine, valproate, and carbamazepine[13].

Atypical antipsychotics such as quetiapine, olanzapine, and aripiprazole are also used. In addition to these drugs, the atypical antipsychotic lurasidone was approved in Japan in 2020 as an effective treatment for depressive symptoms in bipolar disorder[14]. In addition, aripiprazole for long-acting injection has a new indication for the prevention of recurrent manic episodes in bipolar I disorder[15].

Lithium

Lithium is the basic drug used in the pharmacotherapy of bipolar disorder and is listed as the first-line drug in the treatment guidelines of many countries and it is included in the WHO Model List of Essential Medicines (https://list.essentialmeds.org/). In Japan, lithium carbonate is used. Lithium is effective in improving manic and depressive states, preventing recurrence of manic and depressive states, and preventing suicide. However, lithium is associated with many side effects, and because of the proximity of the safe and toxic concentrations, regular measurement of blood levels is necessary. Blood levels should be measured at the beginning of treatment and once every two to three months after stabilization. The effective blood level is between 0.4 and 1.2 mM, and toxicity is more likely to occur when the level exceeds 1.5 mM.

Side effects such as diarrhea, anorexia, thirst, polydipsia, and polyuria are seen when lithium is started. Hand tremor may persist even in the effective concentration range. In the case of intoxication, various symptoms appear, such as cerebellar ataxia, gait disturbance, consciousness disturbance, and vomiting. Since hypothyroidism is often observed, TSH, free T3, and free T4 should be checked regularly. Even if hypothyroidism is observed, lithium treatment can be continued by taking thyroid hormone.

Since concomitant use of non-steroidal anti-inflammatory drugs may increase lithium blood levels, attention should also be paid to concomitant medications. Lithium toxicity is more likely to occur during dehydration. Long-term use of the drug may cause renal dysfunction due to interstitial nephritis, etc. Therefore, a regular check of renal function is necessary. Calcium levels should also be measured periodically while taking lithium, as lithium may cause hyperparathyroidism.

Lithium is contraindicated in pregnancy in Japan due to the increased risk of cardiovascular malformations in the fetus when taken during pregnancy, but it has been reported that there is no significant increase in risk when the dose is 600 mg or less per day[16], and revisions to the drug information are expected.

Various other side effects have also been reported, but due to the limited availability of medications for the treatment of bipolar disorder, we should not give up easily when side effects occur and consider measures to minimize them.

Anticonvulsants

Among the anticonvulsants used as mood stabilizers, lamotrigine alone is indicated for the maintenance treatment of bipolar disorder in Japan. It is effective in preventing relapses and recurrences of all episodes, but the main effect of lamotrigine is to prevent depressive episodes.

Valproic acid has been shown to be effective in manic states. Clinical trials of its prophylactic effect have not been successful, and it does not show a significant prophylactic effect against placebo, and its prophylactic effect is reported to be inferior to that of lithium, but it is also used as a prophylactic drug in clinical practice because meta-analyses suggest its efficacy.

Carbamazepine was found to have an effect on manic states in Japan. Some small trials are suggesting a prophylactic effect, but the evidence is insufficient.

Of these antiepileptic drugs, valproic acid and carbamazepine are indicated by insurance for the measurement of blood levels under the name of manic-depressive illness.

Antipsychotics

For the manic state of bipolar I disorder, many atypical and typical antipsychotics have been effective, as well as lithium, valproate, and carbamazepine.

For the depressive state of bipolar disorder, three atypical antipsychotics, quetiapine, olanzapine, and lurasidone, have been shown to be effective and are indicated in Japan.

Although not covered by insurance, prophylactic effects have been shown for olanzapine, aripiprazole, and quetiapine. The prophylactic effect of quetiapine is mainly for the prevention of depression. In addition, sustained injection of aripiprazole has been shown to prevent relapses and recurrences of bipolar disorder and was covered by insurance in 2020. The preventive effect of aripiprazole is only for the prevention of manic states.

Psychotherapy

Psychotherapy alone is not effective in treating

bipolar disorder. However, psycho-education is essential to help the patient understand the illness and to encourage and assist acceptance of the illness by paying attention to the patient's mental reactions to it[17]. Psycho-education aims to help patients understand the nature of the disease, the effects and side effects of medications, as well as to help them and their families understand and share what the first signs of relapse are. Therefore, it is important to discuss and confirm the initial signs of relapse with the family and share them with the patient and the family. It is also meaningful to predict in advance the stressors that are likely to trigger relapse and to learn how to cope with them.

It is also important to keep a regular life in the treatment of bipolar disorder, as even one-night sleep deprivation can trigger a manic state. Interpersonal social rhythm therapy is reported to be effective in preventing episodes in bipolar disorder. However, it is difficult to receive this treatment in Japan, and usually, the essence of social rhythm therapy is included in psychoeducation; e.g., avoiding staying up all night, get some sunlight in the morning, light exercise such as taking a walk in the morning, and avoiding excessive social stimulation when the mood is unstable.

Cognitive-behavioral therapy (CBT), which is widely used for depression, has also been reported to be effective in preventing the recurrence of bipolar disorder. CBT is available at least in urban areas in Japan.

Etiology

Bipolar disorder has a higher concordance rate in monozygotic twins than in dizygotic twins, so there is no doubt that genomic factors are involved[18]. On the other hand, even in monozygotic twins with almost the same genome, not all of them develop the disease, and it is considered that non-genetic factors such as environmental factors are also involved[19]. Perinatal factors, such as perinatal complications, influenza infection during pregnancy, and smoking of mothers, are reported as environmental factors that pose a risk of bipolar disorder. Early developmental adversity has been reported to have a negative impact on symptoms and course. Stress is said to trigger the onset and recurrence, but it cannot be said to be the cause.

Genome research

As mentioned above, genome-wide association studies (GWAS) have been conducted because of the involvement of genetic factors in bipolar disorder[20]. Sixty-four relevant genomic loci were identified in a GWAS of 41,917 bipolar patients[21]. Among these, *FADS2* (Fatty Acid Desaturase 2) and *FADS1*, which were first found in a GWAS of approximately 3,000 Japanese patients[22], are genes for enzymes involved in the metabolism of unsaturated fatty acids, and their reduced activity has been associated with bipolar disorder. In addition to the calcium (Ca^{2+}) channel gene *CACNA1C*, which was one of the first genes found in the GWAS for bipolar disorder, a new association was found with another Ca^{2+} channel gene, *CACNB2*. The risk genes for bipolar disorder included many genes involved in synapses, Ca^{2+} signaling, and neurogenesis. In addition, many genes encoding target proteins of antipsychotics, antiepileptic drugs, and other drugs were included.

We performed exome analysis in 354 trio families (patients and their parents) of bipolar disorder and analyzed de novo mutations, i.e., mutations that were not present in the parents[23]. As a result, we found that de novo mutations were more common in genes with few loss-of-function mutations in the general population. The loss-of-function de novo mutations were more common in genes such as presynaptic active zones and ion channels. In addition, somatic mosaic mutations were frequently found in genes that cause neurodevelopmental disorders, indicating that the presence of genes that cause neurodevelopmental disorders in a somatic mosaic state may be a risk factor for bipolar disorder.

Neurobiological studies

Although various pathological hypotheses for bipolar disorder have been proposed, the calcium hypothesis, which has been previously reported to be associated with high intracellular Ca^{2+} levels and has been found to be relevant in recent genomic studies, is the most likely. However, since intracellular Ca^{2+} affects many cells, it is difficult to understand the pathogenesis of bipolar disorder by itself[11].

We have been focusing on the relationship between mitochondria and bipolar disorder based

on the results of magnetic resonance spectroscopy in bipolar disorder patients showing impaired energy metabolism and high levels of mitochondrial DNA (mtDNA) mutations in postmortem brains of patients. It has been reported that patients with mitochondrial diseases have a high rate of bipolar disorder (around 20%)[24].

Therefore, we created transgenic mice that express a mutant of polymerase gamma (*Polg*, mtDNA synthetase), one of the genes responsible for mitochondrial disease, only in the brain. The mice exhibited recurrent hypoactive episodes that lasted about two weeks[25]. This condition occurred on average once every six months, and detailed behavioral analysis showed that they met the diagnostic criteria for a depressive episode (loss of interest, sleep disturbance, increased appetite, slow movements, fatigability, and impaired social behavior). During lithium treatment, these episodes became less frequent, and the patients showed increased corticosteroids during the episodes. In addition, tricyclic antidepressants caused manic-like behavioral changes.

To clarify the brain region responsible for this hypoactivity, we searched for brain regions with high accumulation of mtDNA mutations and found the highest accumulation in the paraventricular thalamic nucleus (PVT). When we manipulated the neuronal circuits of the PVT in mice, similar hypo-active episodes appeared, suggesting that the depression in the model mice was caused by dysfunction of the PVT.

The PVT receives strong projections from serotonergic neurons and is a brain region with high serotonin concentration. It is unique in that it projects to both the amygdala, which is involved in the fear, negative emotion and the nucleus accumbens, which is involved in the reward, positive emotion[26].

In another mouse model of mitochondrial disease (*Ant1* mutant mice), serotonin neurons showed hyperexcitability[27]. Hyperexcitability is also suggested in a study of neurons derived from induced pluripotent cells of patients with bipolar disorder[28]. Neurons in the PVT may also be hyperexcitable in the mutant POLG mice described above. If overexcitability of the serotonin neuron-PVT system is involved in the pathogenesis of bipolar disorder, we may be able to understand the pathogenesis of this disorder, which presents depressive and manic states in which both negative and positive emotions are extremely enhanced.

These findings suggest the entire picture of bipolar disorder. Genomic factors result in impaired intracellular Ca^{2+} regulation, which leads to hyperexcitability of emotion-related neural circuits, resulting in impaired emotion/cognition balance[11].

The gene that regulates excitability in the PVT is a T-type Ca^{2+} channel, and valproic acid is known to be its inhibitor.

Among the serotonin receptors, serotonin 5-HT7 receptors have a characteristic distribution of being abundant in the PVT[29], and it is noteworthy that lurasidone is a blocker of serotonin 5-HT7 receptors.

Mechanism of action of therapeutic agents

The most common theory of the mechanism of action of lithium is inhibition of inositol monophosphatase (IMPase). Inhibition of IMPase causes intracellular depletion of inositol, resulting in diminished agonist-stimulated inositol phospholipid metabolism, which results in attenuation of intracellular Ca^{2+} mobilization. It is also suggested that GSK-3β inhibition also plays a role in lithium's action.

In a study that screened compounds that inhibit IMPase, a drug called ebselen was found, and recently it was suggested that ebselen may be effective in the manic state of bipolar disorder[30], which may support the theory that the mechanism of action of lithium is via IMPase inhibition.

On the other hand, for antiepileptic drugs, many attempts have been made to search for common effects with lithium, and intriguing results were obtained. However, no consensus has been reached. Recent genomic studies have found associations with genes involved in neuronal excitability, including Ca^{2+} channels, and iPS cells derived from bipolar disorder patients[28], as well as our studies in animal models, have indicated hyperexcitability of neurons. It makes sense to think that these antiepileptic drugs are acting by modulating neuronal excitability, similarly to their action to epilepsy.

Most antipsychotics antagonize the dopamine D2 receptor, which is thought to be the major mode of action for schizophrenia. Most antipsychotics are also effective in manic states, and their effects on manic states are also thought to be mediated by dopamine D2 receptor antagonism. Atypical anti-

psychotics have fewer extrapyramidal symptoms through a variety of mechanisms, but it is still unclear why some atypical antipsychotics are effective for depressive states in bipolar disorder and others are not. Olanzapine, quetiapine, and lurasidone, which are atypical antipsychotics effective for depression in bipolar disorder, all are antagonists of serotonin receptors, which may be involved in their mechanism of action.

Cognitive-behavioral therapy is a treatment that normalizes the cognitive patterns that predispose to depression, such as overgeneralization and all-or-nothing thinking. These characteristic cognitive patterns are the very characteristic information processing of emotions, and cognitive behavioral therapy may normalize the emotion/cognition balance. Currently, lithium, antiepileptic drugs, atypical antipsychotics, and cognitive-behavioral therapy are often used in combination in clinical situations, and they are thought to act at different points in the pathophysiological pathway of bipolar disorder.

Acknowledgments

This work was partly supported by AMED (JP 20km0405208, JP20dm0207074, 21wm0425006h0001) and JSPS KAKENHI (JP18H05435, JP18H05428).

Funding

No funding to declare.

Author contributions

TK. wrote the manuscript.

Conflicts of interest statement

Dr. Kato reports grants and personal fees from Japan Agency for Medical Research and Development (AMED), grants and personal fees from Ministry of Education, Culture, Sports, Science and Technology (MEXT)/Japan Society for the Promotion of Science (JSPS), during the conduct of the study; personal fees from Kyowa Hakko Kirin Co., Ltd., personal fees from Eli Lilly Japan K.K., grants and personal fees from Otsuka Pharmaceutical Co., Ltd., personal fees from GlaxoSmithKline K.K., personal fees from Taisho Pharma Co., Ltd., grants and personal fees from Dainippon Sumitomo Pharma Co., Ltd., personal fees from Meiji Seika Pharma Co., Ltd., personal fees from Pfizer Japan Inc., personal fees from Mochida Pharmaceutical Co., Ltd., grants and personal fees from Shionogi & Co., Ltd., personal fees from Janssen Pharmaceutical K.K., personal fees from Janssen Asia Pacific, personal fees from Yoshitomiyakuhin, personal fees from Astellas Pharma Inc., personal fees from Nippon Boehringer Ingelheim Co. Ltd., personal fees from MSD K.K., personal fees from Kyowa Pharmaceutical Industry Co., Ltd., grants and personal fees from Takeda Pharmaceutical Co., Ltd., personal fees from Taisho Pharmaceutical Co., Ltd., personal fees from Taisho Toyama Pharmaceutical Co., Ltd., grants and personal fees from Eisai Co., Ltd., grants and personal fees from Mitsubishi Tanabe Pharma Corporation, grants from Teijin Pharma, outside the submitted work.

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Special Reviews

Juntendo Medical Journal
2022. 68(1), 25-30

Mental Health of Healthcare Workers During the COVID-19 Pandemic

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On January 16, 2020, the first case of coronavirus disease 2019 (COVID-19) in Japan was reported. In the spring of the same year, the shortage of personal protective equipment (PPE) such as surgical masks became a significant issue. In addition, the medical staff had to encounter discrimination during this period. Thus, the mental health of these staff has been greatly affected by the social situation, the media coverage of the COVID-19 epidemic, and the shortage of PPE in hospitals.

Various factors make it difficult for the medical staff to seek professional help for mental well-being. Therefore, self-care plays an important role in the prevention of depression and anxiety disorders among healthcare workers. When the healthcare workers face problems in their work environment, they should coordinate with the hospital to promptly improve the system. COVID-19 resulted in new societal norms and changed our lifestyles significantly. Insomnia is a particular issue among healthcare workers. Lifestyle analysis is thus necessary if insomnia needs to be addressed.

Because the opportunities for communication are reduced during the COVID-19 pandemic, conscious communication is essential. During this difficult time, the staff may not receive sufficient guidance from their superiors at work, for example for guidance received by resident doctors from their seniors. This will also provide opportunities to communicate vital information about matters such as infection control. Therefore, quality communication and accurate information should be directed toward all healthcare workers.

Key words: COVID-19, healthcare workers, mental health, pandemic, Japan

Introduction

In the winter of 2019, a new viral pneumonia was detected in Wuhan, China, and the causative pathogen was identified as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). On January 16, 2020, the first case of coronavirus disease 2019 (COVID-19) in Japan was reported. Since then, COVID-19 has spread across the globe. In the spring of the same year, patients began to complain of suspected COVID-19 at their local medical practices based on misinformation about the growing epidemic. Healthcare workers were inundated with demands for tests and treatment. In addition, the shortage of personal protective equipment (PPE) such as surgical masks became a big problem during this period. Many medical institutions had to impose restrictions such as one mask per person per week. The supply of gowns ran out, and aprons fashioned from plastic bags had to be used instead. At that time, there was no cure for the new coronavirus, and infection control guidelines had to be hastily established. Both the "sword" of treatment and the "shield" of PPE proved inadequate against COVID-19.

In addition, there was discrimination against medical staff during this period. Specifically, medical professionals who responded to COVID-19 were bullied in the workplace and discriminated against by children's nursery schools and kinder-

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354th Triannual Meeting of the Juntendo Medical Society "Recent topics in Psychiatry" [Held on sep. 9, 2021]
[**Received Oct. 13, 2021**][Accepted Nov. 4, 2021]
J-STAGE Advance published date: Feb. 4, 2022

doi: 10.14789/jmj.JMJ21-0032-R

gartens, which prohibited these healthcare workers from going to kindergartens.[1] Children of healthcare workers were bullied and harassed, denied admission to nursery schools, and refused carriage by taxi drivers.[2] A study of 10,511 healthcare workers who responded to SARS found that 49% were subject to social criticism and 31% to family inhibition. The damage to mental health among these workers caused by discrimination is a matter that requires attention.[3]

The mental health of medical staff has been greatly affected by the social situation, the media coverage of the COVID-19 epidemic, and the PPE shortages in hospitals. When considering the mental health of medical professionals, it is necessary to address and resolve the problems with society and the work environment.

Self-care of healthcare worker

Various factors can make it difficult to ask for professional help with mental health problems. These include stigma, inactivity, cost, convenience, and the belief that the problem can be resolved alone.[4] Therefore, the prevention of depression and anxiety disorders among healthcare workers requires individual self-care.

The first step in self-care is awareness. The COVID-19 pandemic might be comparable to the Black Death of the 14th century, the cholera outbreak of the 19th and 20th centuries, and the Spanish flu of 1918. The impact this global health crisis has had on mental health is immeasurable. The hard work of healthcare workers across the world deserves a great deal of praise. They are at the forefront of the fight against a global crisis the likes of which are seen once in hundreds of years. It is necessary to understand that worry is a natural response to such a difficult situation. Self-care must include appropriate self-analysis and concrete measures to solve the emotional and practical problems one faces. Work satisfaction is negatively correlated with psychosocial issues so dealing effectively with issues at work is vital to mental health.[5] WHO provides useful guidelines on specific methods of self-care.[6] Interested readers should consult the web link in the reference for further details.

When medical staff encounter problems in the work environment, it is important to coordinate with the hospital to promptly improve the system. This paper will consider the efforts made to address the possible detrimental effects of COVID-19 on mental health among healthcare workers at the Juntendo Clinic of the Juntendo University School of Medicine. These efforts have focused on encouraging self-care among staff. Specifically, this has consisted of self-care through improvements to lifestyle and improved communication. We shall consider each of these in turn.

Improvements in lifestyle

COVID-19 created new societal norms and changed our lifestyles significantly. Insomnia is a particular issue among healthcare workers. There have been numerous reports of insomnia among healthcare workers dealing with COVID-19.[7] Causes of insomnia can include stress, lack of exercise, drinking and smoking, evening caffeine intake, and browsing smartphones and computers before going to bed. Because COVID-19 restricts social activity, individuals find themselves at home more and this can lead to lethargy and inactivity. Lifestyle analysis is necessary if insomnia is to be addressed. Does the individual skip meals or overeat? Do they drink a lot of alcohol alone at home? Are they absorbed in social media until just before going to bed? Such bad habits should be corrected immediately.

To improve quality of life, one must make the conscious decision to "Act-Belong-Commit."[8] "Act" means engagement in activities one enjoys. It may include taking a walk, listening to music, and talking to or spending time with friends. "Belong" refers to engagement with other people; this means belonging to social groups and actively participating in events or hobby groups. "Commit" refers to involvement in, and commitment to, activities, causes, or organizations. Mental health can be maintained by actively engaging in desirable activities to achieve positive life changes.

Excessive exposure to information about COVID-19 during off-hours is not desirable. A great deal of the information about COVID-19 on the Internet is based on insufficient evidence and is often purposely emotive. It is important to switch off one's mind before going to bed to prevent insomnia. It is also necessary to consciously select the information to which we attend. Healthcare workers dealing with COVID-19 during working hours should take particular care to avoid too much attention to the

topic outside of work to ensure a good balance between work and private life. Individuals exposed to disasters often read and watch more media coverage of the event than others.[9] This is probably an attempt to better understand the events they have been affected by but it can be detrimental to mental health to overexpose oneself to such negative information. A Chinese study of the COVID-19 pandemic found that more exposure to COVID-19 social media coverage was associated with more adverse effects, anxiety, and depression among adults.[10] To create a clear distinction between work and private life, healthcare workers should avoid COVID-19 news at home and immerse themselves instead in enjoyable activities and hobbies.

Improvements in communication

Since opportunities for communication are reduced during the COVID-19 pandemic, it is necessary to communicate consciously. If stress accumulates and there is no opportunity to discuss work worries and complaints, it can be difficult to maintain a healthy mentality. During this difficult time, there may be insufficient guidance available from work superiors, for example for residents from senior doctors. It is advisable to try to create opportunities for regular communication between higher and lower-ranking members of staff, including new employees. This will also provide opportunities to communicate vital information about matters such as infection control.

It is important to provide all staff with quality communication and accurate information updates. Explanations should be clear, honest, and frank, and every effort should be made to implement procedures that help everyone to work safely and comfortably. It also provides staff with opportunities to discuss their experiences, provide mutual support, and increase social cohesion.[11] Smooth communication should be optimized not only between senior and junior staff but also between colleagues.

Employees who live alone may feel emotionally isolated and it is important to encourage these workers to maintain regular connections with family and friends. In a cross-sectional study in China, medical staff living alone during the COVID-19 pandemic reported significantly higher depressive symptoms than those living with others.[12] A study of Japanese medical institutions also found that the depressive symptoms of healthcare workers tended to decrease as the number of cohabitants increased.[13] For this reason, daily communication with others is important to the prevention of depression.

Support for healthcare workers at Juntendo University Hospital

At Juntendo University Hospital, we have secured adequate supplies of vital COVID-19 medical items such as PPE. It is important to stockpile supplies for potential emergency situations in advance and we must not spare money to protect our staff. Staff care issues should not be underestimated, and it is desirable to take prompt action when problems occur. Staff care issues include salary, working hours, vacations, and breaks. Under busy circumstances and in crisis situations such as COVID-19, it is desirable to avoid salary cuts. In addition, since the COVID-19 pandemic is expected to be an issue in healthcare for some time, it is important to reduce overtime as much as possible and create a workplace atmosphere that encourages all employees to take vacations.

The health management office of Juntendo University Hospital has provided counseling and mental health support for healthcare workers in high-stress departments. Employees who develop depression often lack the motivation or drive to seek the help they need on their own. When staff develop mental health issues and take a leave of absence, it can take time to recover, so it is in the interests of the organization as well as its employees for the employer to take the initiative in preventing depression. The mental health department of Juntendo University Hospital has enhanced the available support system in response to the pandemic to ensure it can always respond to staff issues related to COVID-19. Psychiatric consultation is recommended because it is often necessary to prescribe psychotropic drugs for employees who have marked insomnia and apparent deterioration in daytime performance, or are suffering from depressed mood or anxiety.

The results of the 2021 mental health check at our hospital

This observational cohort study was conducted in June 2021 as part of a mandatory health check of

Juntendo University Hospital employees (Tokyo, Japan). A total of 4,350 participants completed a web-based questionnaire on their medical history and current health status. The Center for Epidemiologic Studies Depression Scale (CES-D) was used for assessment, with a score of ≥16 considered indicative of depression. The study protocol was approved by the Ethics Committee of the Juntendo University Faculty of Medicine (approval no. 22004). Informed consent was obtained from all participants. Statistical analyses were performed using SPSS v. 22 (IBM Corp., Armonk, NY, USA). Chi-square tests were performed to assess correlations between depression scores and patient characteristics (e.g., sex). Clinical variables were compared using two-tailed Mann-Whitney U tests in cases with two groups or the Kruskal-Wallis test in cases with three or more groups. A two-tailed p-value of <0.05 was considered significant for all tests.

Correlations between variables associated with the CES-D scores were subjected to univariate analyses.

In this study, the prevalence of depression among all employees was 30.8% in 2021, and significantly greater than the pre-pandemic value in 2019 of 27.5%. When participants were subdivided by occupation (nurses, paramedics, doctors, residents, clerks, researchers, support staff, teaching staff, and part-time staff), nurses had the highest depression rate (41.5%), followed by clerks (33.4%), support staff (32.7%), paramedics (31.9%) , and researchers (27.2%), whereas teaching staff (21.8%), residents (20.7%), doctors (20.2%), and part-time staff (17.1%) reported lower depression rates (Table 1).

Table 1 Comparison of 2021 and 2019 CES-D results for Juntendo University Hospital employees (Tokyo, Japan).

	Outcome of CES-D		
	2021	2019	
	N = 4350	N = 4240	p-value
Sex, M/F	1603/2747	1633/2607	0.114
Age, years	37.8 ± 12.1	37.8 ± 12.1	0.812
Number and the positive rate of CES-D by occupation			
doctor	604 (20.2%)	611 (18.0%)	0.343
resident	87 (20.7%)	98 (19.4%)	0.856
nurse	1329 (41.5%)	1295 (40.0%)	0.427
paramedics	499 (31.9%)	501 (30.5%)	0.682
support staff	110 (32.7%)	100 (30.0%)	0.766
clerk	467 (33.4%)	397 (28.7%)	0.142
teaching staff	280 (21.8%)	241 (14.9%)	0.055
researcher	688 (27.2%)	648 (20.5%)	**0.005**
part-time	286 (17.1%)	349 (15.2%)	0.516
Average score by occupation			
doctor	9.0 (4.0 – 14.0)	6.0 (2.0 – 12.0)	**<0.001**
resident	10.0 (6.0 – 14.0)	6.5 (2.0 – 12.25)	**0.005**
nurse	13.0 (8.0 – 21.0)	13.0 (6.0 – 20.0)	**0.002**
paramedics	12.0 (7.0 – 18.0)	10.0 (5.0 – 17.0)	**0.002**
support staff	13.0 (8.0 – 18.0)	10.0 (5.25 – 7.75)	0.175
clerk	11.0 (6.0 – 18.0)	9.0 (4.0 – 16.5)	**0.008**
teaching staff	8.0 (3.0 – 14.0)	5.0 (2.0 – 11.0)	**<0.001**
researcher	10.0 (6.0 – 16.0)	8.0 (3.0 – 13.75)	**<0.001**
part-time	7.0 (3.0 – 12.0)	5.0 (2.0 – 11.0)	**0.006**

p values with statistical significance are in bold.
The Center for Epidemiologic Studies Depression Scale, CES-D.

CES-D scores were significantly positively correlated with age ($p < 0.0001$) and sex ($p < 0.0001$). In addition, occupation was associated with CES-D score changes between 2019 and 2021 ($p = 0.001$). The results from binary logistic regression analyses for the score changes between 2019 and 2021 showed that female staff, younger employees, and nurses have a higher risk of depression among Japanese health workers (Table 2). This result is similar to that of previous studies overseas. Luo identified female sex, nursing, and financial poverty as risk factors for anxiety and depression among healthcare workers during COVID-19.[14] Xiong also found associations between psychological stress and being female, being under 40, having existing chronic mental illness, and being unemployed in a systematic review.[15] The hypothalamic–pituitary–adrenal (HPA) axis was found to be sex-specific; therefore, stress responses differ between men and women.[16] Neurobiological and immunological sex differences are also noted, and women are about twice as likely to be depressed as men.[17]

Nurses were at the forefront of COVID-19 practice and had high infection and mortality rates.[18–19] Approximately 10.1% of people infected with COVID-19 are health care workers, and guidance on infection control and mental care for nurses is necessary.[20] Nurses, who are mostly women, may have been more prone to depression as they work in the close proximity of patients with COVID-19. Therefore, adequate mental health care may be particularly vital for young female nurses.

Conclusions

The COVID-19 pandemic has put all healthcare workers under a great deal of psychological stress. To prevent depression in this population, it is important to raise awareness of self-care practices that improve lifestyle habits and increase communication. Younger generations of workers and specific healthcare occupations such as nurses are more vulnerable to depression at this time and require more support.

Acknowledgments

The authors thank Enago (www.enago.jp) for carefully proofreading the manuscript.

Funding

This study was funded by the Juntendo Mental Health Institute (2020-003).

Author contributions

NK contributed to the conceptualization, design, and writing of this manuscript.

Table 2 Factors related to CES-D results as determined by logistic regression analysis.

	Odds ratio	95% CI	p-value
Sex			
female	1.18	(1.05–1.32)	**0.007**
male	1		
Age, years	0.98	(0.98–0.99)	**<0.001**
Occupation			
doctor	1.21	(0.93–1.56)	0.156
resident	0.97	(0.63–1.48)	0.882
nurse	2.59	(2.03–3.30)	**<0.001**
paramedics	1.98	(1.54–2.56)	**<0.001**
support staff	2.32	(1.62–3.33)	**<0.001**
clerk	2.12	(1.64–2.75)	**<0.001**
teaching staff	1.31	(0.96–1.78)	0.086
researcher	1.38	(1.07–1.77)	**0.012**
part-time	1		

p values with statistical significance are in bold.
The Center for Epidemiologic Studies Depression Scale, CES-D.

Conflicts of interest statement

The author declares no conflicts of interest.

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Health Topics for Tokyoites

Juntendo Medical Journal
2022. 68(1), 31–35

Osteoporosis and Osteoporotic Vertebral Fractures: Breaking the Chain of Osteoporotic Fractures to Increase Healthy Life Expectancy

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Osteoporosis is an important issue related to life expectancy and healthy life expectancy in Japan, where the super-aging population is growing. Currently, in Japan, some kind of assistance is needed for an average of 10 years at the end of life. In many cases the reason assistance is needed is loss of mobility due to a fracture caused by a fall. When people suffer one fracture due to osteoporosis, they are also more likely to have another fracture, which is called a secondary fracture. Breaking the negative chain of fractures is very important in osteoporosis. In addition, if patients suffer a loss of mobility due to a compression fracture of the spine, this activity cannot be regained even if the fracture is healed. To prevent this from happening, it is also important to heal fractures rapidly, so that patients can quickly return to normal life, thus extending healthy life expectancy.

Key words: osteoporosis, secondary fracture, osteoporotic vertebral fractures

Introduction

Osteoporosis is an important life-threatening problem in Japan, where there is a growing super-aging population. Patients with osteoporosis are more likely to suffer fractures, such as osteoporotic vertebral fractures (OVF), proximal femur fractures (neck or trochanteric fractures of the femur, PFF), proximal humerus fractures (PHF), and distal radius fractures (DRF) (Figure 1). It has been reported that patients who suffer OVF and PFF in their 60s have a more than ten-fold increased risk of death for up to 2 years[1]. More specifically, patients who are unable to walk due to a PFF often suffer from various other diseases such as pneumonia, resulting in a 5-year survival rate of 26%. This survival rate is lower than those for liver and stomach cancers. Extending life expectancy is the most important theme in medicine, but we believe that extending healthy life expectancy is just as important. Currently, in Japan, people need some help for an average of 10 years at the end of life, and the reason for needing assistance is more often immobility due to musculoskeletal disorders than weakness due to dementia or old age. In this context, the Japanese Orthopaedic Association (JOA) proposed the term 'locomotive syndrome' to designate a condition requiring nursing care or the risk of developing such a condition, following a decline in mobility resulting from one or more disorders of the locomotive organs, which include the bones, joints, muscles, and nerves[2]. Even if such support is needed, it is expected that there will be a shortage of manpower in Japan, where one in three people will be 65 or older in 2030. Therefore, we must do all we can to prevent fractures and immobility.

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46th Health Topics for Tokyoites "To survive the 100-year life -Aiming for health and longevity-" [Held on Feb. 20, 2021]
[**Received Sep. 12, 2021**][Accepted Sep. 27, 2021]
J-STAGE Advance published date: Nov. 12, 2021

doi: 10.14789/jmj.JMJ21-0025-R

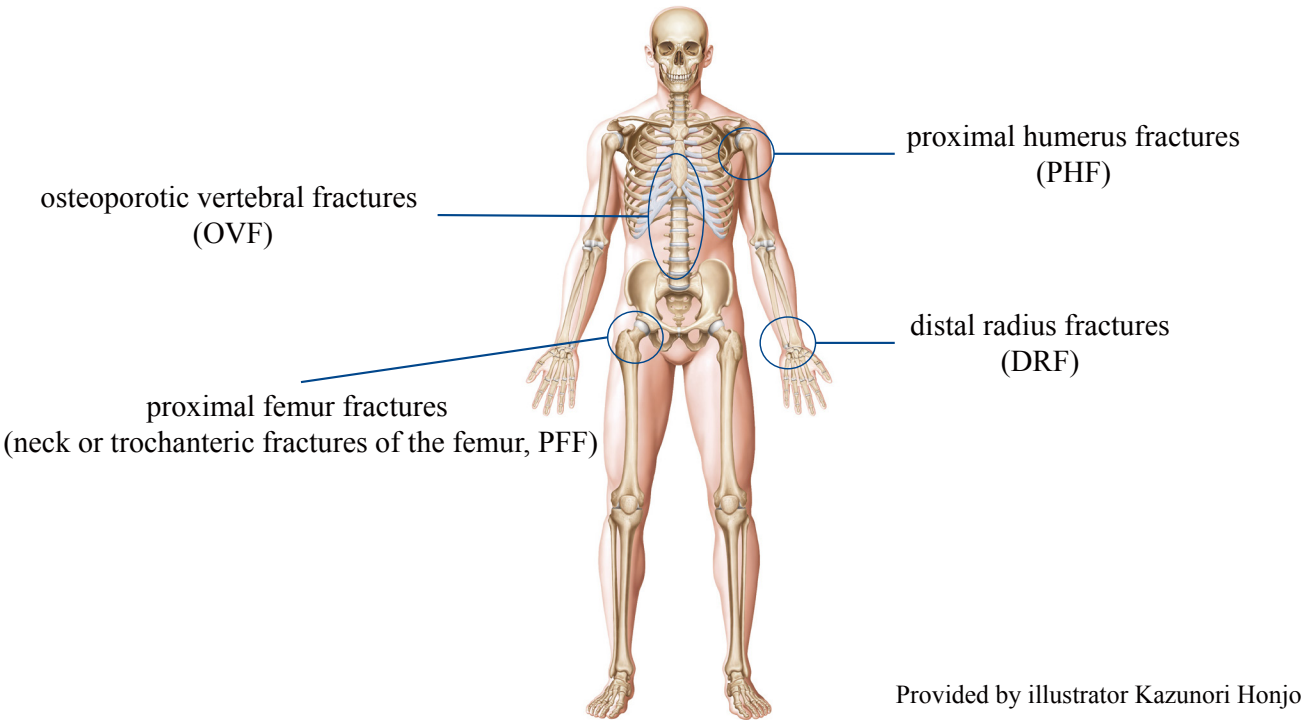

Figure 1 Common sites of osteoporotic fractures

Secondary fracture

When an osteoporotic fracture occurs, the patient is also more likely to have another fracture. This is called a secondary fracture, and the secondary fracture causes the next fracture, forming a negative chain. For example, in OVF, if a patient suffers from one OVF, the probability of suffering a second OVF is 2.6 times higher, and if there are two OVF, the probability of suffering a third OVF is five times higher[3]. Similarly, for PFF, the risk of developing a contralateral PFF after one PFF is four times higher than in the general population. Moreover, it is known that one in five people who have a fracture will suffer one on the other side within a year. Guidelines for the prevention of this secondary fracture have now been created. According to these, patients with an OVF or PFF are recommended to start medication for osteoporosis, and when a patient suffers from another osteoporotic fracture, drug treatment is to be initiated if evaluation of bone mineral density (BMD) shows a value of 80% or less of the young adult mean (YAM). It has been reported that the risk can be reduced to less than half by secondary fracture prevention[4]. Based on this, we investigated the current status of prevention of secondary fractures due to osteoporosis at our institution (Table 1). The subjects were patients who suffered osteoporotic fractures (OVF, PFF, PHF or DRF) between August 2015

Table 1 Percentages of patients undergoing tests for osteoporosis and receiving treatment after osteoporotic fractures

	OVF	PFF	DRF	PHF
Percentage of patients in whom bone density and/or bone metabolism markers were measured after fracture (%)				
2015.8–2016.7	58.8	34.0	15.4	50.0
2018.10–2019.2	54.1	11.8	14.3	0
Percentage of patients who received osteoporosis treatment after fracture (%)				
2015.8–2016.7	75.0	36.2	38.5	50.0
2018.10–2019.2	70.3	23.5	28.6	8.3

and July 2016. We examined whether osteoporosis tests (BMD and/or bone metabolism marker measurement) were performed after the injury and whether osteoporosis treatment was administered. We found that the proportions of patients in whom BMD and/or bone metabolism markers were measured after fracture were: OVF, 58.8%; PFF, 34.0%; PHF, 15.4%; and DRF, 50%. Similarly, the proportions of patients who received osteoporosis treatment after fracture were 75.0%, 36.2%, 38.5%, and 50.0%, after OVF, PFF, PHF and DRF respectively. In Japan, the rate of treatment for secondary fracture prevention after osteoporotic fracture has been reported to be around 15%[5, 6], so our results were an improvement. However, we considered that it was necessary to be more proactive in preventing secondary fractures, and thus further strengthen measures against osteoporosis. Consequently more appropriate treatment was commenced according to the guidelines. Then, after the measures were initiated, the same survey was conducted again. The subjects of this survey were patients with the same fractures as above between October 2018 and April 2019. The results showed that the proportions of patients in whom BMD and/or bone metabolism markers were measured after fracture were 54.1%, 11.8%, 14.3%, and 0%, respectively, in the OVF, PFF, PHF and DRF groups, and the proportions given osteoporosis treatment after fracture were 70.3%, 23.5%, 28.6% and 8.3%, respectively. All percentages were below those recorded in the first survey, which made us keenly aware of the difficulty of countermeasures. This depended on the doctor's enthusiasm for treating osteoporosis, so it is necessary to create a system that can be continued regardless of the doctor in charge.

There have been other reports of the difficulty of continuing osteoporosis treatment. In a survey of 67,101 patients who received initial administration of osteoporosis drugs in Hokkaido, Japan, from January 2014 to December 2015, it was reported that the retention rate after 1 year was 38.7% and that after 2 years it had fallen to only 7.7%[7]. At our institution, we surveyed patients who planned to continue weekly osteoporosis treatment for two years in principle, and found that 36.7% of patients quit in just one month, and only 6.7% were able to continue for two years. To understand why patients could not continue with the treatment, we conducted a telephone survey of 39 patients who had stopped taking the medication. The result revealed that elderly people are often unable to attend their appointments due to other diseases. Interestingly, it was also found that 11 patients had discontinued their medication on their own initiative due to concerns about COVID-19. This is a very important issue, because some treatments for osteoporosis can lead to a reduction in BMD and even an increased risk of fractures if left untreated after discontinuation[8, 9]. Therefore, it is important to continue treatment for osteoporosis. However, the essence of osteoporosis treatment is not to take medicine to increase BMD, but to prevent fractures and prevent immobility due to fractures. Treatment of osteoporosis is not limited to drugs, but there have been studies involving interventions such as reducing the incidence of OVF by strengthening the back muscles and increasing BMD by walking[10, 11].

Osteoporotic vertebral fractures (OVF)

The incidence of OVF has been found to increase rapidly after age 65[12]. Patients with OVF suffer from two stages of pain. At first, about two months after the injury, the patient complains of sharp pain upon waking, but says it doesn't hurt much if they are sleeping or upright. This is because the fractured part moves when they wake up. Treatment at this stage is to put on a brace to stabilize the fracture and to start medication to promote bone formation. It should be noted that OVF can sometimes be severe, and the collapsed vertebral body can compress the spinal cord and cauda equina nerves, causing paralysis and requiring major surgery. However even if this is not the case and the fracture can be stabilized, the second stage of pain will inevitably follow. Many of the patient's complaints at this time are "I get stiff, hurt, and lean forward when I'm standing or walking for a long time. I want to hold something. It's easier to have a cart for shopping." This is a low back pain due to muscle fatigue caused by a rounded back due to OVF. This pain is related to the structure of the pelvis and spine. In Japanese patients, the pelvis is tilted forward at approximately 45 degrees. The lumbar spine is lordotic when standing straight in that state. The angle of lordosis is approximately 45 degrees, which is the same as the tilt of the

pelvis. When an OVF occurs, the lumbar spine loses its shape and straightens. In response to this, the pelvis tilts forward naturally. This is a condition in which the pelvis compensates for the decrease in lordosis of the lumbar spine. If another OVF occurs in this state, the lordosis of the lumbar spine disappears, and in some cases, the lumbar spine may progress to kyphosis. At this point, the pelvis can no longer compensate and the entire body is tilted forward. In order for people in this state to stand upright, they need to use their back muscle to the fullest. However, this causes the back muscle to become tired after a while. This spinal deformity may be surgically cured, but it is so invasive that it is not practical for most older people. Therefore, the patient must accept this condition. For patients with such conditions, we recommend resting when in pain, sitting when working in the kitchen, and using a walker. This is the state of "locomotive syndrome" mentioned above. Before reaching this state, OVF need to be healed quickly. People have been found to lose 3% of their muscle strength after resting for a day. Decreased activity leads to reduced life expectancy and reduced healthy life expectancy.

What does it mean to heal an OVF quickly? It is important to relieve the pain quickly, for the patient to be able to move from an early stage, and to return to their normal life without losing muscle strength. One of the quickest treatments is an operation called balloon kyphoplasty (BKP) (Figure 2). The crushed bone is inflated with a balloon and cement is injected, allowing the patient to stand and walk the day after surgery. The fracture can be cured very quickly, but in most cases surgery is not immediate due to the amount of preparation required. We have investigated how to cure an OVF quickly. Specifically, we compared the period of improvement in pain caused by OVF between a group treated with BKP and a non-surgery group. The results showed that the average time from the onset of pain to improvement was 12.7 weeks in the surgery group and 10.0 weeks in the non-surgery group, which means that the pain improved faster without surgery. The problem with this is that it takes a long time to perform surgery, and it makes no sense to have surgery early. In fact, other studies have shown that people who have undergone BKP are less likely to develop other illnesses and have a longer lifespan than those who have been cured without surgery[13–15]. This shows the importance of quickly healing an OVF. Summarizing the treatment of OVF, the initial pain can be expected to improve in about 10 weeks without surgery. During that time, if the patient is unable to move due to pain, the patient's

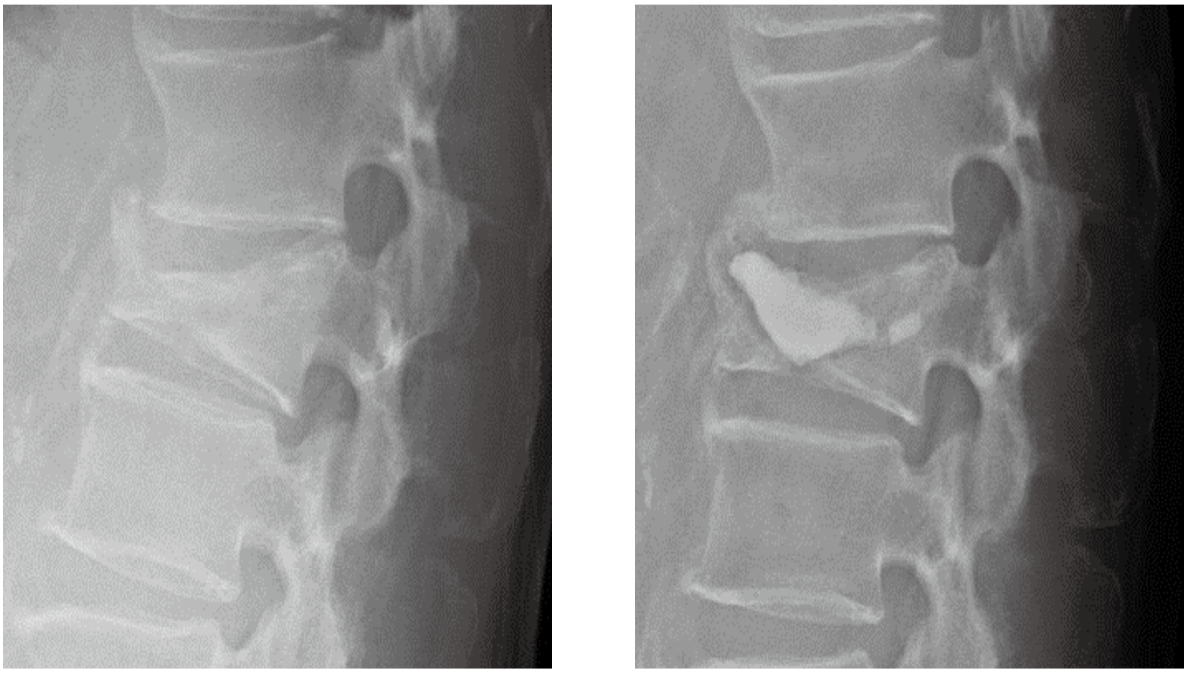

Figure 2 Balloon kyphoplasty for osteoporotic vertebral fracture

muscle strength and quality of life will deteriorate and cannot be restored. In that case, early surgery should be considered.

In conclusion, it is important to take measures to prevent subsequent fractures from occurring due to osteoporosis, and it is also important to heal a first osteoporotic vertebral body fracture as soon as possible to allow the patient to return to their normal life.

Acknowledgments

Not applicable.

Funding

No funding was received.

Author contributions

RM analyzed and interpreted the patient data, and was a major contributor in writing the manuscript.

Conflicts of interest

The author declare that there are no conflicts of interest.

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Original Articles

Juntendo Medical Journal
2022. 68(1), 36–43

The Impact of Travel Distance to Delayed Presentation and Follow-up Attendance of Retinal Detachment Cases in Surabaya, Indonesia

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Objectives: To assess the delayed presentation of Retinal Detachment (RD), its association from travel distance to the referral hospital (TDH), the period from symptom onset to consultation (SO–C), Proliferative vitreoretinopathy (PVR) severity, and 6 months follow–up attendance (6mo–FA).

Method: A retrospective review based on medical records. Age, sex, initial best–corrected visual acuity (BCVA), TDH, SO–C, PVR type, and 6mo–FA were recorded. Multivariable ordered logistic regression was used to analyze the association between TDH and SO–C, and SO–C and PVR severity. Multivariable logistic regression was used to analyze 6mo–FA according to TDH. Multiple linear regression was used to assess the association between initial BCVA and TDH. Age and sex were included in all multivariable adjustments.

Results: A total of 387 patients had RD with 59.2% predominantly males and the mean age±SD was 46.3±13.9 years. The initial BCVA of less than 3/60 was 81.1%. The averages of SO–C and TDH were 183.5±456 days and 160.9±364 km, respectively. The TDH of more than 120 km distance was significantly associated with longer SO–C (adjusted OR 1.78; CI 95% 1.09–2.92). PVR was noted in 17.6% of patients. The SO–C of 31–60 days was significantly associated with PVR severity (adjusted OR 4.28; CI 95% 1.47–12.51). The TDH of more than 120 km distance was significantly associated with 6mo–FA (adjusted OR 0.46; CI 95% 0.27–0.93).

Conclusions: Long TDH was significantly associated with a longer period from symptom onset to consultation and 6mo–FA. Hence, accessible eye care is essential to refer RD cases in a timely fashion.

Key words: retinal detachment, delayed presentation, symptom onset, follow–up attendance, health system, accessible

Introduction

Permanent blindness is often caused by retinal disease, glaucoma, and other disorders that present late or with insufficient care[1)]. Furthermore, delay in bringing retinal detachment (RD) cases to retinal specialists tends to be a trend in developing countries, the treatment of which has been a minor priority[2)]. Lack of education, access, and inadequate healthcare coverage are probable contributing factors[3)]. At many stages in the healthcare phase, delays between first symptoms and surgical repair may occur, which can be either from the doctor or the patient[4)]. In one study from Indonesia, childhood RD was revealed to often arrive late for assessment[5)]. Other studies pointed out that patients

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〔**Received Sep. 7, 2021**〕〔Accepted Nov. 5, 2021〕
J–STAGE Advance published date: Feb. 4, 2022

doi: 10.14789/jmj.JMJ21–0024–OA

are more likely to delay the examination and appear as complex RD[2, 3]. This is similar to other findings that suggest that later and severe RD cases appear to emerge from more deprived regions. This pattern has significant effects on the final visual prognosis[6].

Retinal detachment can be estimated at 17,500 to 25,000 new cases annually in Indonesia. However, the national annual report for the number of RD surgeries is not provided[1]. In Indonesia, approximately 1,600–2,800 vitreoretinal doctors are expected to serve 230 million people. Given the small number of VR surgeons in Indonesia, especially now that the population has reached 270 million, treating VR diseases requires not only timely intervention but also easier access to referral healthcare centers and affordability[1]. Healthcare access is also impacted by transportation, especially in rural regions where travel distances are long and alternative forms of transportation are few[7, 8].

While retinal detachment has added to the burden of blindness in Indonesia, few studies have directly discussed their epidemiology and effects on the scale of retinal diseases. In this paper, we will study what has been learned about RD in developing countries with limited facilities and uneven vitreoretinal surgeon distribution. We would like to identify the situation particularly at Dr. Soetomo General Academic Hospital (DSGAH) as one of the national referral hospital in Indonesia that located in East Java. East Java has two other hospitals that are equivalent to DSGAH, however comprehensive vitreoretinal facilities are inadequate. The purpose of this research was to study discrepancies between travel distance to the referral hospital (TDH) as one of the socioeconomic factors that impact the referral pathway. We hypothesized that patients living far from the referral hospital will be more likely to seek treatment late, which would lead to more severity and having unfavorable compliance in completing follow-up treatment. As such, late referral, the longer period from symptom onset to consultation (SO-C), and severe retinal proliferation occurrence might impact the final visual acuity (VA). These findings will hopefully provide the data to enhance access to eye care, lead to better screening programs in peripheral areas, and raise awareness not only for health workers but also the people at risk so that early identification and diagnosis can be achieved as timing is a critical factor in RD management.

Methods

Material and Methods

A retrospective medical chart review was conducted at the Ophthalmology Out Patient Department (OPD) of Dr. Soetomo General Academic Hospital (DSGAH), Surabaya, East Java, Indonesia from 2013–2017. DSGAH is one of two other national referral hospital in East Java that serves as a teaching hospital and a referral center for the east part of Indonesia. The review was performed on all cases diagnosed with RD by the consultant in the vitreoretinal unit. Approval to review the medical record was obtained from DSGAH Institutional Review Board (IRB) under the number 0977/ KEPK/ II/ 2019. All the procedures performed in this study were in accordance with the ethical standards of the Declaration of Helsinki and the IRB. The IRB committee has been informed of the objective of the study and how the data will be used. As this study presented no risk to the participants and did not violate individual rights, thus access to medical records has been granted without informed consent needed.

Demographic details including age, sex, travel distance to the referral hospital (TDH), the period from symptom onset to consultation (SO-C), Proliferative vitreoretinopathy (PVR) severity, and 6 months follow-up attendance (6mo-FA) were obtained. The TDH was determined by the distance between the place of origin (where the patient lives) and DSGAH Surabaya in kilometer (km) using an online distance calculator. The SO-C was determined by patients' subjective reports in the medical record, which defines the period between the first onset of retinal detachment symptoms such as floaters, photopsia, visual field defect or vision disturbances, and the first examination at OPD.

The presenting BCVA and 6 months post-operative BCVA from the affected eye were recorded from Snellen's charts examination and converted to LogMAR for analysis. Proliferative vitreoretinopathy (PVR) type according to the Updated Retina Society Classification (1991)[9] and macula condition (macula-on or macula-off) were retrieved. Additionally, 6mo-FA was obtained from the availability of the data in the medical records, including anatom-

ical retinal reattachment in 6 months post-operative and 6 months postoperative BCVA.

Statistical Analysis

Travel distance to the referral hospital (TDH) was classified into 5 groups, less than or equal to 30 km, 31-60 km, 61-90 km, 91-120 km, and more than 120 km. SO-C was categorized into 5 groups, less than or equal to 7 days, 8-14 days, 15-30 days, 31-60 days, and more than 60 days. Further, PVR type was classified as type 0 (No PVR), type 1 (PVR grade A and grade B), and type 2 (PVR grade C). The results were reported as mean and standard deviation for quantitative variables and percentage for categorical variables. Univariate and multivariable ordered logistic regression models were used to estimate the crude and adjusted odds ratios (ORs) and their 95% confidence interval (CIs) for SO-C according to TDH, and PVR severity according to SO-C. The Brant test of parallel regression assumption was used to test whether the relationship between each pair of outcome groups was the same. A nonsignificant test statistic provided evidence that the parallel regression assumption had not been violated. We used univariate and multiple linear regression analysis to estimate the crude and adjusted coefficients and their 95% CIs to assess the association between initial BCVA and TDH. Furthermore, the univariate and multivariable logistic regression model was used to estimate the crude and adjusted ORs and their 95% CIs for 6mo-FA according to TDH. In all multivariable adjustments, age and sex were included. IBM SPSS version 23 and Stata version 15 (StataCorp, College Station, TX, USA) were used to perform all the statistical analyses. P values <0.05 were considered statistically significant.

Results

Retinal Detachment (RD) found in 387 patients consisted of 229 (59.2%) males and 158 (40.8%) females, with the age range of 7-76 years (mean± SD: 46.3±13.9 years) (Table 1). The majority of the patients (359; 92.8%) came from Java Island. Of the 387 patients, 172 (44.4%) came from a distance of less than or equal to 30 km from DSGAH, and 94 (24.3%) were from a distance of more than 120 km (Table 1). The mean ± SD travel distance to the referral hospital (TDH) was 160.9±364 km with a median of 52 (10-2819) km. The mean ± SD period from symptom onset to consultation (SO-C) was 183.5±456 days with a median of 30 (2-3775) days. When broken down into categories, most patients came with a SO-C of more than 60 days (128; 33.1%) (Table 1). After the adjustment for age and sex, compared to the TDH of less than or equal to 30 km, only the TDH of more than 120 km distance was significantly associated with a longer SO-C (adjusted OR 1.78; 95% CI 1.09-2.92) (Table 2). The result of the brant test for proportional odds assumption was not statistically significant (p = 0.31), indicating that this method of analysis was appropriate for this study.

Proliferative vitreoretinopathy (PVR) prior to surgery was noted in 17.6% (13.9-21.7) patients consisting of PVR grade A-B (39; 10.1%) and C (29; 7.5%), while most of the cases (225; 58.1%) were without PVR. After the adjustment for age and sex, compared to the SO-C of less than or equal to 7 days, only the SO-C of 31-60 days was significantly associated with advanced PVR type (adjusted OR 4.28; 95% CI 1.47-12.51) (Table 3). The result of the brant test for proportional odds assumption was not statistically significant (p = 0.34), indicating that this method of analysis was appropriate for this study. Macula off presented in 274 (70.8%: 95% CI 66.0-75.3) patients.

Table 4 shows the visual acuity at the time of the initial examination and after the 6-month follow-up. The initial BCVA of less than 3/60 (LogMAR 1.3) was most encountered (81.1%). The mean initial BCVA was LogMAR 1.96±0.58 (range: LogMAR 0.0-3.0). The mean BCVA 6 months after surgery was LogMAR 1.42±0.59 (range: LogMAR 0.1-2.7). Table 5 presents the results of linear regressions to evaluate the association between initial BCVA and TDH. After the adjustment for age and sex, no significant association was evident between initial BCVA and TDH.

Of the 387 patients, 72 (18.6 %: 95% CI 14.9-22.8) could be followed up for 6 months. Table 6 shows the results of logistic regressions to evaluate the association between TDH and 6 months follow-up attendance (6mo-FA). Again, only the TDH of more than 120 km was significantly associated with 6mo-FA (adjusted OR 0.46; CI 95% 0.27-0.93).

Table 1 Demographic of retinal detachment patients in Surabaya, Indonesia. (N=387)

Demography Characteristics	Value
Sex (n,%)	
Male	229 (59.2)
Female	158 (40.8)
Age (years)	
Mean ± SD	46.3±13.9
Median (range)	49 (7-76)
Place of Origin (n,%)	
Java Island	359 (92.8)
Outside of Java Island	25 (6.5)
Unknown	3 (0.8)
Travel distance to the referral hospital (TDH) (kilometers)	
Mean ± SD	160.9±364
Median (range)	52 (10-2819)
TDH Categories (n,%)	
≤30 km	172 (44.4)
31-60 km	45 (11.6)
61-90 km	32 (8.3)
91-120 km	41 (10.6)
>120 km	94 (24.3)
unknown	3 (0.8)
Period from symptom onset to consultation (SO-C) (days)	
Mean ± SD	183.5±456
Median (range)	30 (2-3775)
SO-C Categories (n,%)	
≤7 days	61 (15.8)
8-14 days	46 (11.9)
15-30 days	74 (19.1)
31-60 days	32 (8.3)
>60 days	128 (33.1)
Unknown	46 (11.9)
PVR grade (n,%)	
Type 0 (No PVR)	225 (58.1)
Type1 (Grade A-B)	39 (10.1)
Type 2 (Grade C)	29 (7.5)
unknown	94(24.3)
Macular condition (n,%)	
On	63 (16.3)
Off	274 (70.8)
Unknown	50 (12.9)

Discussion

The small number of cases in this study (387 patients) despite the fact that DSGAH is one of the national referral hospital, might be due to the period when this study was carried out was when the referral system in the era of National Health Insurance in Indonesia has been implemented with new regulations. As such, DSGAH has been receiving particularly advanced cases referred from primary or secondary level health facilities. In this study, we observed that travel distance to the referral hospital (TDH) especially of more than 120 km was significantly associated with a longer period

Table 2 Odds ratios of travel distance to the referral hospital (TDH) on the period from symptom onset to consultation (SO-C) by multivariable ordered logistic regression.

TDH	Crude Odds Ratio	95% CI	P-value	Adjusted Odds Ratio	95% CI	P-value
≤30km	reference			reference		
31-60 km	1.32	0.71-2.49	0.38	1.35	0.71-2.56	0.35
61-90 km	0.66	0.33-1.33	0.25	0.67	0.33-1.35	0.26
91-120 km	1.49	0.78-2.86	0.23	1.49	0.77-2.89	0.23
More than 120 km	1.73	1.06-2.81	0.03	1.78	1.09-2.92	0.02

Table 3 Odds ratios of the period from symptom onset to consultation (SO-C) on PVR severity by multivariable ordered logistic regression.

SO-C	Crude Odds Ratio	95% CI	P-value	Adjusted Odds Ratio	95% CI	P-value
≤7 days	reference			reference		
8-15 days	1.86	0.71-4.87	0.21	1.75	0.66-4.65	0.26
16-30 days	1.20	0.46-3.15	0.70	1.22	0.45-3.27	0.70
31-60 days	4.02	1.39-11.58	0.01	4.28	1.47-12.51	0.01
> 60 days	0.99	0.42-2.36	0.99	1.02	0.43-2.44	0.96

Table 4 Initial BCVA and 6-month follow-up BCVA.

VA Category (n,%)	Initial BCVA	6 mo follow-up BCVA
> 6/18 (< LogMAR 0.5)	11 (2.8%)	5 (1.3%)
6/18-6/60 (LogMAR 0.5-1)	23 (5.9%)	13 (3.4%)
6/60-3/60 (LogMAR 1-1.3)	20 (5.2%)	19 (4.9%)
< 3/60 (> LogMAR 1.3)	314 (81.1%)	44 (11.4%)
Unknown	19 (4.9%)	306 (79.1%)
VA mean and median (LogMAR)		
Mean ± SD	1.96 ± 0.58	1.42 ± 0.59
Median (range)	2.3 (0.0-0.3)	1.48 (0.1-2.7)

Table 5 Coefficients of travel distance to the referral hospital (TDH) on initial BCVA by multiple linear regression.

TDH	Crude coefficients	95% CI	P-value	Adjusted coefficients	95% CI	P-value
≤30km	reference			reference		
31-60 km	0.01	-0.19-0.20	0.94	0.02	-0.17-0.22	0.81
61-90 km	-0.06	-0.29-0.17	0.61	-0.05	-0.27-0.18	0.69
91-120 km	0.13	-0.07-0.33	0.19	0.15	-0.05-0.36	0.14
≥120 km	-0.11	-0.25-0.04	0.16	-0.11	-0.26-0.04	0.16

Table 6 Odds ratios of travel distance to the referral hospital (TDH) on 6 months follow-up attendance (6mo-FA) by multivariable logistic regression.

TDH	Crude Odds Ratio	95% CI	P-value	Adjusted Odds Ratio	95% CI	P-value
≤30km	reference			reference		
31-60 km	0.74	0.32-1.71	0.48	0.68	0.29-1.61	0.39
61-90 km	1.14	0.47-2.73	0.77	1.07	0.44-2.59	0.88
91-120 km	0.47	0.17-1.29	0.14	0.44	0.16-1.21	0.11
≥120 km	0.50	0.25-1.01	0.05	0.46	0.27-0.93	0.03

from symptom onset to consultation (SO-C) and only SO-C 31-60 days was associated with PVR severity, yet dose-response relationship was not appeared. This might be due to information bias, unevenly distributed samples in each category or some unmeasured confounding factors. The TDH of more than 120 km was significantly associated with 6mo-FA. This finding reflects that travel distance may impact the willingness of the patient to complete their follow-up treatment in addition to other socioeconomic reasons. However, the result obtained in this study demonstrated that TDH of more than 120 km did not prevent 6mo-FA, this might be influenced by the area of origin, its development index, infrastructure and transportation system availability.

As mentioned by Mitry et al., cases from more deprived regions appear to present later with extensive detachments and have significant implications for the final visual prognosis[10]. Longer period from symptom onset to consultation was associated with PVR severity in our study was also mentioned in previous studies[11, 12]. Age, gender[11] and ethnicity[12, 13] strongly affected the incidence of RD. In this study, the male population was predominant as also seen in several studies[11, 12, 14, 15]. In terms of age, our result was in agreement with Chandra et al., that RD may occur at a younger age in Asians (46.1 years) as indicated in other studies[13, 14, 16, 17]. The above results, even after adjustment for age and gender in the multivariate analysis, suggest the importance of the impact of distance to the healthcare facility on RD care. In Indonesia, the distance of more than 120 km to the healthcare facility in some areas is a burden especially when the areas are not traversed by an adequate transportation system. Meanwhile, not all residents in the peripheral area have private vehicles or can afford to arrive by plane; some of them have to wait for their family members to drive them. This problem was also mentioned by Kelly et al. and Mattson: in rural areas, great travel distance, less public transportation, and inconvenient transportation schedule could play a significant role[7, 8]. There is still a tendency to use private vehicles for mobilization within and between cities in Indonesia. During this research period, the development of intercity buses between provinces on the island of Java hasn't been experienced growth and fluctuated[18] despite the fact that the Indonesian government has been accelerating infrastructure development in transportation especially the highway construction and railway transportation services improvement[19].

The majority of the patients in this study presented late and had their macula off. This was in line with other studies in developing or third world countries, i.e., many RD patients presented late, which varied from about 2 weeks[4, 20] more than one month[21, 22], and more than 3 months after the onset of symptoms[3, 20]. As such, eyes with a long RD duration had significantly poorer visual acuity both at the initial and follow-up examinations[23]. Another study in Southwest Ethiopia showed many things in common with our study in terms of the average travel distance for patients (average travel distance of 87.5 km±120.7 km) and PVR severity significantly associated with delay in presentation[22]. A study in Kwazulu-Natal revealed that few patients returned for follow-up or re-open, which meant that the definite success rate was uncertain[2]. This represents variations in the complexity of the cases, facilities, retina specialist distribution, and willingness for the treatment follow-up.

The likely contributory factors in the delayed presentation include patients' personal factors, facilities, and doctors' delays. The patients' factors include long travel distance[24], lack of knowledge[3] or unfamiliarity of the symptoms[3, 25-27], lack of affordability[20, 24], lack of health insurance or coverage for the limited procedure[20] and lack of awareness[24, 26, 28, 29]. As mentioned in other studies, patients from peripheral areas might first attend their nearest optometrist[4, 30] and consider the elongated distance[4, 24] and were referred elsewhere before presenting to the referral center[4, 30]. While most of our patients arrived late for many reasons including long travel distances, lack of financial and ignorance of symptoms, the distance they would have to travel to the tertiary hospital affects their decision. This includes transportation fees, accommodation expenses, and meal allowance for their companions during treatment, especially when the patients require hospitalization for surgical procedures that may take several days or weeks. Additional sources of late presentation are scarcity of facilities[24] and clinical resources[3], lack of primary eye care[2, 24] and lack of vitreoretinal surgeons[20, 24].

In this study, patients from peripheral areas, in addition to their cultural backgrounds, prefer to visit their local nurse or general practitioner first at a primary care unit since general ophthalmologists with adequate facilities are also limited. Those considerations might contribute to longer SO-C. Although accurate cut-off for the macula-off duration and RD duration to intervention is difficult to determine, the majority are in agreement that the macula-off duration is inversely proportional to visual recovery[30,31]. Therefore, urgent interventions to shorten macula-off RD duration may provide better long-term VA results[32].

This study has several limitations in terms of its retrospective nature that comes from single center. During the study period, transition from manual to electronic medical record was applied and contributed to our inability to collect complete sociodemographic data including education level, per capita income, human/area development index and other important information related to patient's delay, doctor's delay or referral system's delay that could have been unmeasured confounding factors to this study. The TDH was determined roughly from the center of the place of origin (where the patients came from) to the referral hospital. The SO-C was obtained only from the patient's subjective report, while not every patient remembered when the symptoms appeared for the first time, as photopsia, floaters, or visual disturbance. The existence of recall bias should be noted. There were several unknown data in PVR grade and macula conditions.

Despite all limitations, this research supports RD epidemiological evidence in a real-world setting and provides an overview of RD in one referral hospital in Indonesia that lacks a vitreoretinal specialist and facilities in certain areas of Indonesia that result in late presentation. In addition to the aforementioned, this study will help us to learn about the availability of facilities for patients that can shorten the referral mechanism, which could benefit patients. Further prospective research regarding risk factors in late RD presentation, whether from the patient's or doctor's delay and scarcity of facilities need to be revealed. For example, a questionnaire regarding the knowledge and awareness of RD patients and their association with final anatomical and functional outcomes should be conducted for evaluating the referral routes and obstacles from the primary care provider to the tertiary eye care unit.

In summary, this study observed that a travel distance of more than 120 km is significantly associated with the longer period from symptom onset to consultation and 6 months follow-up attendance. The aforementioned is significantly associated with PVR severity that may result in redetachment and poor prognosis. In order to improve the final VA outcome, it is essential to refer RD cases in a timely fashion to prevent any delays, especially in macula-on RD. Furthermore, the government needs to enhance access to eye care and develop novel approaches to provide accessible and affordable healthcare in peripheral areas. Additionally, continuing medical training and raising awareness in relation to RD emergency for frontline health workers as well as education for patients or people at risk are expected. Along with the development in social media, the importance of RD as one of ophthalmic emergency could be delivered through webinars and many platforms of social media both for health workers and people at risk.

Acknowledgements

The authors would like to thank Vitreoretinal Division Department of Ophthalmology, Faculty of Medicine Universitas Airlangga/ Dr. Soetomo General Academic Hospital, Surabaya (Dr. Ima Yustiarini, SpM and Dr. Ady Dwi Prakosa, SpM), Dr. Ifan Romadhon Lukmana, SpM, Dr. Diana Yuliawati, SpM, Dr. Andira Bulan Nandinanti and Siti Rukayah, for their contribution to this study.

Funding

The authors received no financial support for the research.

Author contributions

The conception and design of the study : SAW, YH. Acquisition of data : SAW, MF. Analysis and interpretation of data : SAW, YH. Writing original draft : SAW. Review and editing critically for important intellectual content : YH, KO. Final approval of the version to be submitted : WS, AM.

Conflicts of interest statement

The Authors declare that there are no conflicts of interest.

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Reviews

Juntendo Medical Journal
2022. 68(1), 44–51

A Contribution to the History of Japanese Education Systems for Radiological Technologists

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Background: The evolution of radiological technology is one of the most remarkable events of modern medical technology. Radiological examination has resulted in non-invasive, individual diagnostic imaging, which has contributed significantly to successful medical treatment of patients.

Key Concepts: This review summarizes past and current Japanese educational systems for radiological technologists with a historical perspective focusing on three periods. The first period begins with Roentgen's discovery of X-rays (1895), the second period begins with the establishment of the Radiological X-ray Technologist Act (1951), and the third period begins with the launch of the first university course for radiological technologists (1987). It is conceivable that those periods are in accordance with the technological paradigm shifts, including the development of contrast radiography and the application of CT and MRI to clinical practice. To maintain awareness of the most recent available technologies and maximize safety, educational programs teaching the latest knowledge were offered during each period.

Conclusions: The advanced technologies require highly skilled radiological technologists and highly established educational systems. At present, over 70% of Japanese educational programs for radiological technologists are university courses leading to a bachelor's degree. The increasing globalization of radiological technology requires future radiological education systems to have a global perspective.

Key words: radiological technologist, education system, history, globalization

Introduction

Radiological technology is essential for high-quality modern healthcare and is used at present not only for diagnostic imaging but for radiation therapy and nuclear medicine. X-ray examinations, introduced at the end of the 19th century, were the first type of non-invasive diagnostic imaging applied to clinical settings[1)]. Before the advent of X-ray technology, the inside of the human body had been visualized for diagnosis of diseases by cadaveric autopsy only after death[1)]. Incorporation of X-ray examination into clinical practice allowing *in vivo* visualization of the human body contributed significantly to successful treatment[2)].

Radiological examinations were initially applied for morphological diagnoses of, for example, orthopedic patients and patients with tuberculosis[2)]. The safety and quality of contrast media have been improved, leading to advances in the field of contrast radiography. Later, two remarkable cross-sectional diagnostic imaging technologies, computed tomography (CT) and magnetic resonance imaging (MRI), were developed in the 1970s to 1980s. Radiological examinations have been gradually substituted for the autopsy as the diagnostic means.

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〔**Received Sep. 14, 2021**〕〔Accepted Sep. 28, 2021〕
J-STAGE Advance published date: Dec. 17, 2021

doi: 10.14789/jmj.JMJ21-0028-R

Radiological technology is highly developed in Japan, with patients frequently undergoing diagnostic radiological examinations. According to the Organization for Economic Co-operation and Development (OECD), the numbers of MRI and CT units per person in Japan are the highest among all countries surveyed[3]. The advanced technologies require competent, skilled radiological technologists (RTs). Education systems updated to fit technological advances are crucial to train skilled RTs and to maintain their knowledge of the latest clinical practices. The transition of the education system is, therefore, a reflection of the development of radiological technology.

This review summarizes past and current Japanese education systems for RTs with a historical perspective focusing on three periods. Based on the educational and technical development, we determined that the first period begins with Roentgen's discovery of X-rays (1895), the second period begins with the establishment of the Radiological X-ray Technologist Act (1951), and the third period begins with the launch of the first four-year university course for radiological technologists (1987). During the first period, Shimadzu X-Ray Technology Training Center (the current Kyoto College of Medical Science), the first X-ray technical education institution in Japan, was established. In the beginning of the second period, Radiological X-ray Technologist Act and X-ray technologist training school designation rule were enacted. In this period, Chuoh College of Medical Technology, the oldest training institution in Tokyo was established in 1959. Since the third period, technological development of radiological technology has been accelerated. Today, there are three types of training schools, universities, professional training colleges, and a training institution run by Japan Self-Defense Forces, comprising a total number of 55 institutions. The universities are accredited by Ministry of Education, Culture, Sports, Science and Technology (MEXT), and all courses are standardized by Ministry of Health, Labour and Welfare (MHLW). The Domestic Radiological Technologist Education Facility Council that oversees those 55 institutions contributes to standardization and improving the education level of RTs.

The present review attempted to reveal historical events in the education system of radiological technology, using several re-discovered references. The article also discusses future perspectives of Japanese radiological technology and RTs. Literature on the Japanese history of radiological technology and publications discussing the educational systems are scarce, and to our best knowledge, this is the first English article to describe the Japanese education system for RTs within a historical context.

1) Beginning of 20th century: Including Roentgen's discovery of X-rays (1895)

A few months after the discovery of X-rays by Wilhelm Conrad Röntgen at the end of 1895, two Japanese groups successfully produced radiographic photographs[4], with one of the first radiographic photographs, showing Japanese swords, published in a journal in April 1896[5]. Initially, medical use of X-rays in Japan occurred in the military[6]. Dr. Eijiro Haga, an army surgeon at that time, reported using X-ray examinations in 1901 in the treatment of soldiers wounded during the Boxer Rebellion[7]. X-ray equipment used at field hospitals was highly regarded during the Russo-Japanese War (1904-05)[4,8]. The early technologies used in radiography were described in an article published in 1906[8]. By using a 110 V DC 70 cm inductor, X-ray images of the limbs required 3 to 4 minutes and images of the chest, thigh, and head required 10 minutes8. Changing the photographic plates significantly shortened the exposure time, to 5 to 30 seconds for the limbs and 15 to 60 seconds for the chest, spine, and thighs[8].

In the early 1910s, X-ray radiology was taught at several military medical schools[6]. Knowledge and methods of radiology were also taught in apprenticeships at universities, hospitals, and clinics[6]. The importance of education about radiological technology was well recognized by the 1920s. The first two publicly available education programs for radiological technology in Japan were organized by Tokyo Denki (the current Canon Medical Systems Corporation) in 1918 and Shimadzu Corporation in 1921[6,9]. The contents of the latter can be assumed from X-ray lecture records published by Shimadzu corporation in 1923. They comprise nine volumes by various authors among whom most held academic titles in medicine, engineering, and science[10]. Among 86 articles in the volumes, the authors of 59 were medical doctors who contrib-

uted topics related to clinical practice. Among the other articles are topics including introduction of X-rays and X-ray tubes, physics, electricity, and X-ray generators[10]. Shimadzu Corporation, a manufacturer of precision, measuring, and medical instruments, produced the first medical X-ray equipment in Japan[9]. A seminar organized by Shimadzu Corporation was the foundation of Shimadzu X-Ray Technology Training Center, the first X-ray technical education institution in Japan (established, 1927). It is believed that the number of X-ray technologists in Japan was 500 to 700 by the end of the Taisho era (1912–1926)[11]. As demonstrated in Figure 1, the number of training institutions known today is few in this period. This indicates that many technologists were trained in various different programs, which were not standardized by the national authority.

2) Mid-20th century: Including establishment of the Radiological X-ray Technologist Act (1951)

The increases in the numbers of radiological examinations during the middle of the 20th century resulted in the profession of RT becoming widely recognized and established in Japan. Following several difficult years required for reconstruction after World War II, the establishment of the profession of RT began in the 1950s. The Radiological X-ray Technologist Act was enacted in 1951, and a two-year educational program accredited and standardized by MHLW was started the next year[12]. The first national examination for X-ray technologists took place in 1954. Prior to that, the first national examination designed for accreditation of those working as medical X-ray technologists was held in 1952. Because of increases in radiological applications in medicine, the Radiological X-ray Technologists Act was renewed as the Radiological Technologist Act in 1968[13], with the first national examination for RTs taking place the same year and continuing since then. The education program was gradually extended from two to three-years in Junior College (Table 1, Figure 1).

During this period, a remarkable event in radiological technology was the emergence of contrast radiography. Egas Moniz, a Portuguese neurosurgeon, discovered contrast angiography in 1927, enabling the imaging of cerebral blood vessels and vascular alterations as well as other intracranial disorders[14]. Two years later, Reynaldo dos Santos, another Portuguese physician, introduced translumbar aortography[15]. Following further developments in angiography, it began to be used in clinical applications. An innovative method using a catheter to gain vascular access, was introduced in 1953. This method, called the Seldinger technique, enabled angiography to be performed safely[16]. Angiography has since been applied to excretory urography, the thoracic aorta, coronary vessels, the renal artery, and the diagnosis of aortic aneurysms[15, 17, 18]. Interventional radiography (IR), first introduced in 1967, is a low-invasive procedure widely used for both diagnostic and treatment purposes[19]. IR initially involved the use of X-ray fluoroscopy, but methodological advances have enabled IR to be performed using a combination of CT and ultrasound[20].

Improvements in the safety and quality of

Table 1 Historical milestones of the Japanese education system for radiological technologists

Year	Event
1918	Start of an educational program for radiographers by Tokyo Denki
1921	Start of an educational program for radiographers by the Shimadzu Corporation
1927	Establishment of the first X-ray technical education institution in Japan
1951	Enactment of the X-ray Technologist Act
1952	Start of a 2-year educational program accredited by the MHLW First national examination for non-certified X-ray technologists
1954	First national examination for X-ray technologists (terminated in 1984)
1956	Termination of the national examination for non-certified X-ray technologists
1968	Enactment of the Radiological Technologists Act First national examination for Radiological Technologists
1987	Establishment of the first bachelor's program for Radiological Technologists by Fujita Health University

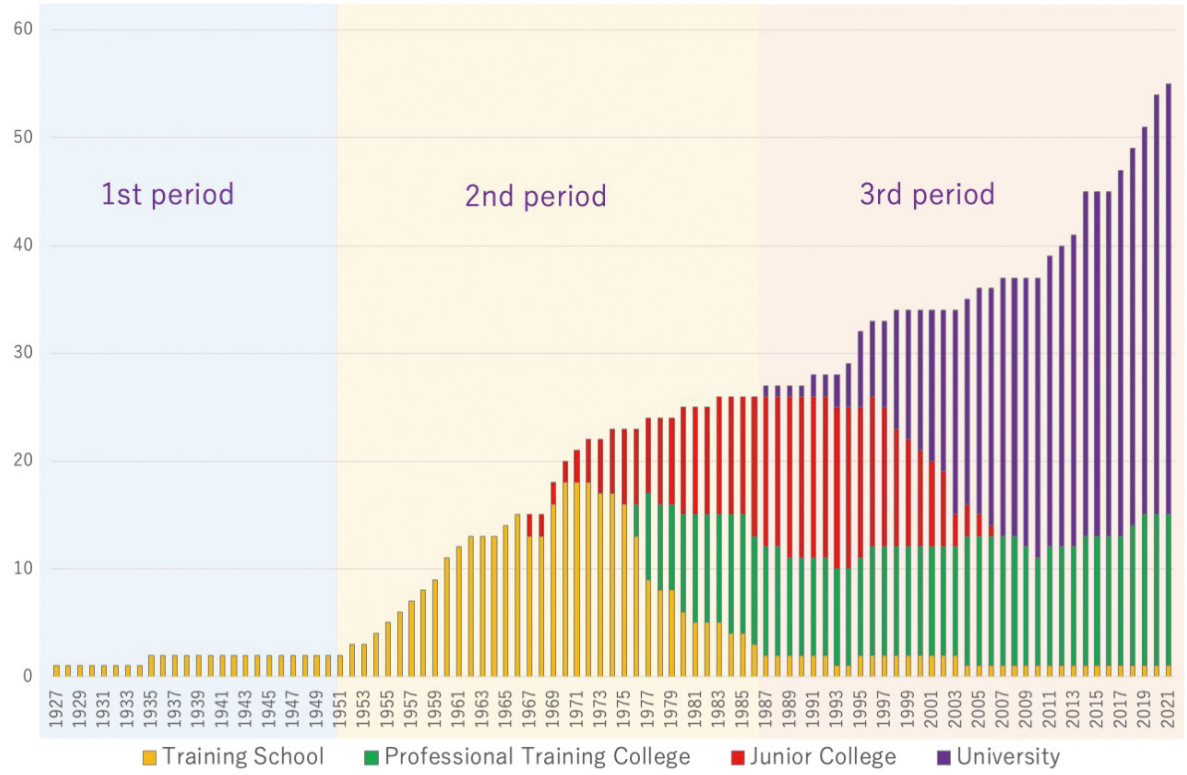

Figure 1 Transition in the education systems in radiological technologists from 1927 to 2021
The number of institutions is retrieved according to the institutions that are currently active. There may have been institutions that existed in the past but were not included because of the lack of records.

contrast media are associated with the evolution of contrast radiography[15]. In the 1950s and 1960s, iodine-based contrast media were used, causing many side effects, including pain, dizziness, and occasional death[21]. Non-ionic contrast media were introduced in the 1970s, initially applied to myelography[21]. As alternatives to these hyperosmolar contrast media, low-osmolar contrast media were developed in the 1980s, significantly reducing the incidence of side effects[21].

Another historically important clinical application of contrast radiography is double-contrast radiography using barium[22]. In Japan, routine examinations for the early detection of gastric cancer using an X-ray fluoroscopy were introduced in the 1950s[23,24], with nationwide examinations continuing for decades[25]. At present, routine screening for early gastric diseases involves double-contrast radiographic examinations combined with gastrointestinal tract examinations by endoscopy[24].

3) Late 20th century to date: Including the launch of university courses for radiological technologists (1987)

The introduction of CT and MRI into clinical practice in the late 20th century was one of the biggest paradigm shifts in radiological examinations. X-ray CT was introduced by an English electrical engineer, Godfrey Hounsfield, who received a Nobel Prize in 1979 for the development of this remarkable technology[26]. To accrue data, an X-ray tube and a detector are arrayed on the opposite sides of a circle, which spins around the patient's body[26]. In Japan, the first CT was installed in Tokyo Women's Medical University Hospital in 1975[27]. The initial CT machines were only for the head, with each scan taking 4 minutes[28]. The scanning method evolved to shorten the time required to scan the entire body. Shifting from a pencil beam to a narrow fan beam shortened the scanning time to 20 seconds, after which the technique was altered from translate/rotate to rotate/rotate methods[28]. In the late 1980s, a helical scan was introduced, which moves the bed while rotating

the X-ray tube and detector array[28, 29]. Detector arrays improved from single to multiple detectors placed in collimation, enabling the scanning of a wide range of the body with many cross-section images in each rotation[29]. At present, a scan from the chest to the pelvis takes a few seconds, and the use of CT over the last few decades has become widespread. The combination of CT or MRI with positron emission tomography (PET), has led to the widespread use of PET-CT and PET-MRI examinations since the 1990s. Conformation radiotherapy that requires the three-dimensional information of the irradiation site rapidly emerged in the early 1980s, upon the clinical application of CT[30]. The development of a CT apparatus specialized for the treatment planning system launched in 1984, with clinical application began in 1987[30].

The impact of new technology on the curriculum of educational programs in RT can be observed by evaluating trends in the national examination. Figure 2 illustrates the number of questions related to CT and MRI in the national examination from 1976 to 2021. Questions related to CT and MRI emerged in the spring of 1977 and the spring of 1986, respectively, with the number of questions gradually increasing since then. From 2011 to 2021, the average numbers of questions per year related to CT and MRI were 13.1 and 20, respectively. In the past decade, the questions related to CT or MRI constituted approximately 17% of the 200 questions on the national examination.

In parallel with advances in these technologies, the role of RTs has expanded, with a wider range of subjects included in educational programs. This led to the introduction of university courses for RTs, the first offered by Fujita Health University in 1987, followed by Suzuka University of Medical Science in 1991 and Osaka University in 1993[31]. The transition to the university courses in this period is shown in Figure 1.

As of 2021, 55 institutions provide educational programs for RTs in Japan, with 40 (73%) of these institutions providing university level courses, and 15 (27%) providing 3-year courses[32, 33]. Of these 15 institutions, 14 are professional training colleges, and one is Institute of Medical Radiology Technologists run by Japan Self-Defense Force (JSDF) (Table 2)[33]. Universities offer bachelor's degrees, and professional training colleges offer diplomas equivalent to associate degrees[34]. National examinations are held once a year and are open to anyone who has completed a program at a univer-

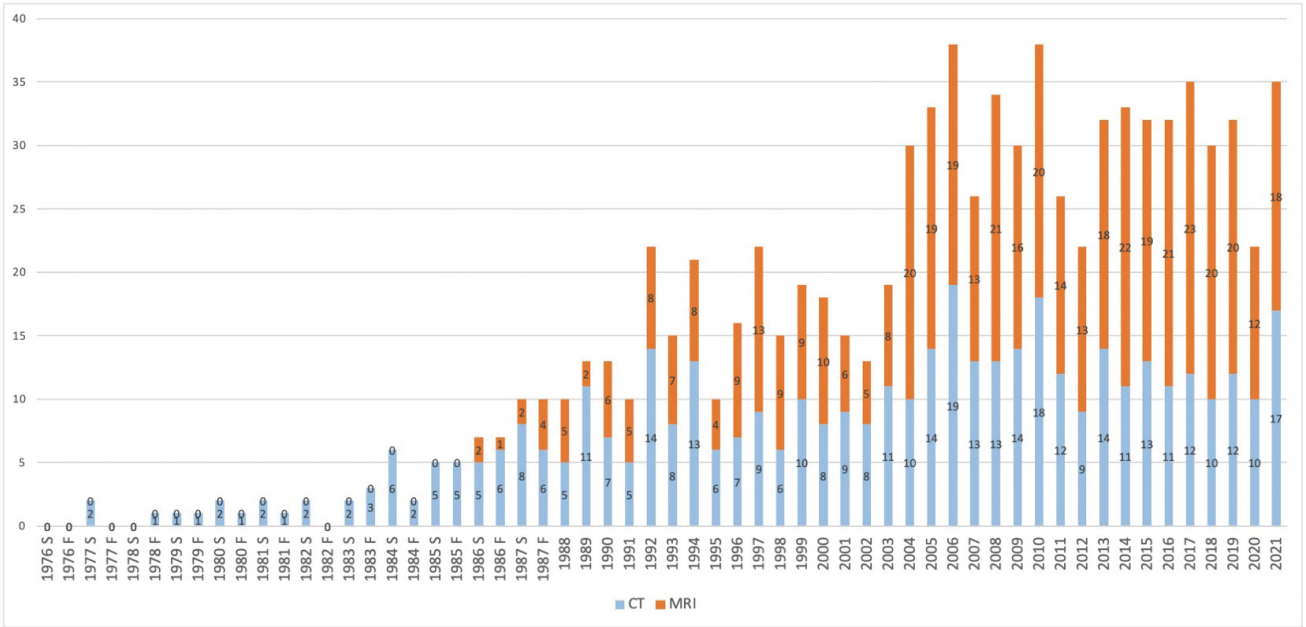

Figure 2 Number of questions related to CT or MRI on national examinations (1976 to date)
Until 1987, the examination was conducted twice a year. S: spring examination; F: fall examination. Data from 1976 to 1977, from 1978 to 1982, from 1983 to 1985, from 1986 to 1989, from 1990 to 1994, and from 1995 to 2000 were obtained from the 1979, 1984, 1987, 1990, and 2000 editions, respectively, of the National Examination Questions (Kanehara shuppan). Data from 2001 to the present were obtained from National Examination Questions (Iryo kagaku sha)

Table 2 Number of educational institutions for radiological technologists (as of 2021)

	Course duration (yrs)	Numbers of institutions by type				
		National	Public	Private	Other	Total
University	4	11	3	26	0	40
Professional training college	3	0	0	14	0	14
Japan Self-Defense Forces	3	0	0	0	1	1

sity, professional training college, or JSDF. Some professional training colleges offer nighttime programs, enabling students to work during the day. Moreover, some students have already obtained a bachelor's degree by the time they enroll in a professional training college. A few professional training colleges will probably remain in the future as they meet the needs of some students.

The curricula of all institutions are standardized and regulated by MHLW[35], and moreover, universities are accredited by MEXT. Of 47 prefectures in Japan, 26 have educational institutions offering these programs, with Tokyo having the most, 10, including five universities; four professional training college, and the JSDF training institution. In addition, Osaka has six institutions, including three universities and three professional training colleges; Hokkaido has four (three and one, respectively), Fukuoka has four (three and one, respectively), and Aichi has three (two and one, respectively).

Future perspectives

Medical services must be of high quality, accessible, and affordable. Simultaneous attainment of these three conditions is barely accomplished in Japan with the contribution of the Japanese healthcare system, in which almost 100% of the population is insured[36]. The World Health Organization (WHO) has stated that, in general, Japanese hospitals are well equipped with high-technology medical devices, including CT and MRI scanners, and that the costs of these examinations are relatively low[36]. In addition, patients in Japan are not restricted by any gate-keeping system, allowing them to choose any hospital or clinic[36]. Consequently, many Japanese patients, even those with mild symptoms, often go to secondary healthcare facilities that have advanced equipment[36]. Increased attendance at these facilities would therefore require an increase in the number of RTs. The MHLW reported that, in 2017, the number of RTs in the workforce was 54,213, or 1.7% of the total number of healthcare workers, 3,124,321. Over the last 30 years, the number of RTs has increased by 1500 to 2500 each year (Figure 3), with the number predicted to increase to 9.5% in 40 years[37].

Aging of the population and emergence of new infectious diseases such as COVID-19 are expected to accelerate developments in radiological technology. The Japanese education system for RTs has evolved in accordance with the needs of Japanese society. However, the increased globalization of healthcare settings will require that the education system attain a global perspective. For example, new digital technologies, such as artificial intelligence (AI) and machine learning, in diagnostic imaging are being intensively studied and becoming competitive. International research collaboration is essential for the development of these emerging technologies[38]. Future university educational programs should therefore foster RTs with a global mindset.

Conclusion

The Japanese education system for RTs has evolved in accordance with technological developments. To maintain awareness of the most recent available technologies and maximize safety, educational programs teaching the latest knowledge were offered during each period. At present, over 70% of Japanese educational programs for RTs are university courses leading to a bachelor's degree. The increasing globalization of radiological technology requires future radiological education systems to have a global perspective.

Acknowledgments

The authors thank Ms. Rio Imai for her help in the preparation of the reference documents. We also thank Juntendo University Academic Media Center (Library) for their professional assistance.

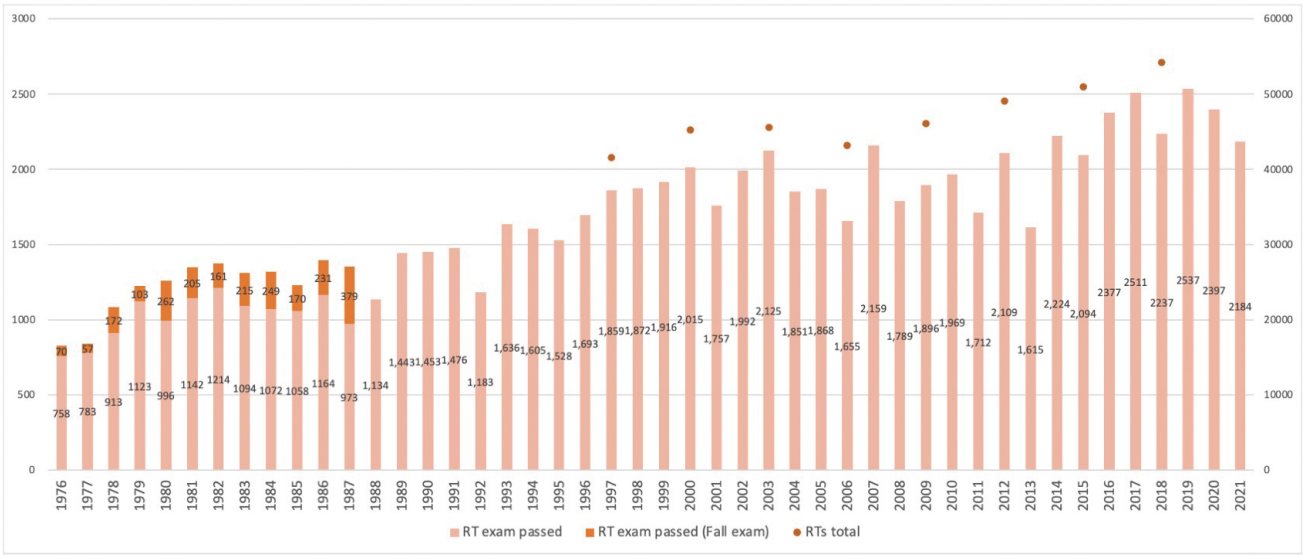

Figure 3 Numbers of RT candidates who passed the national examinations and total numbers of RTs in the workforce by year (1976 to date)
Until 1987, the examination was conducted twice a year (spring and fall). Data from 1976 to 1977, from 1978 to 1982, from 1983 to 1985, from 1986 to 1988 were obtained from 1979, 1984, 1987 and 1990 editions, respectively, of the National Examination Questions (Kanehara shuppan). Data from 1989 to the present were obtained from the MHLW website (https://www.mhlw.go.jp/file/05-Shingikai-10801000-Iseikyoku-Soumuka/0000200803.pdf)

Funding

This research did not receive a grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contributions

YS devised the project and the main conceptual ideas. KM and MG collected and analyzed the data regarding the radiologist education. HS and SK proved and interpreted the data. YM performed reference investigations and wrote the first draft. TS provided the data regarding the radiologist schools and refined the manuscript. HD supervised the project. All authors provided critical feedback and helped shape the research. All authors read and approved the final manuscript.

Conflict of interest statement

The authors declare that they have no conflicts of interest regarding this review.

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Mini Reviews

Juntendo Medical Journal
2022. 68(1), 52–59

Latest Clinical Evidence and Operative Strategy for Small-Sized Lung Cancers

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Many thoracic surgeons revealed that consolidation tumor ratio or solid component size on thin-section computed tomography has been considered more prognostic than maximum tumor size in non-small cell lung cancer (NCSLC). According to the results, the 8th TNM classification drastically changed the staging system, i.e., clinical T category was determined based on the invasive or solid component size excluding a ground-glass opacity (GGO). However, several debates are arising over the application of radiological solid size for the clinical T staging. Meanwhile, recent several institutional reports have noticed a significantly simple fact that the presence of a GGO denotes an influence on the favorable prognosis of NSCLC. More important, radiologic pure-solid lung cancers without a GGO exhibit more malignant behaviors with regard to both the clinical and pathological aspects, and show several histologic types that have a poorer prognosis than radiologic part-solid lung cancer. In contrast, favorable prognostic impact of the presence of a GGO component was demonstrated, which was irrespective of the solid component size in cases in which the tumor showed a GGO component. Recently, this concept has been gradually noticed on a nationwide level.

Obvious distinctions regarding the several baseline characteristics between the tumor with/without GGO component is a fundamental biological feature of early-stage lung cancer, which would result in a big difference in prognosis, modes of recurrence, overall behavior, and appropriate operative strategies. As a future perspective, the presence or absence of a GGO should be considered as an important parameter in the next clinical T classification.

Key words: lung cancer, ground-glass opacity, surgery

Introduction

Since the Japan Clinical Oncology Group (JCOG) study prospectively validated the radiological definition that enabled prediction of the pathological noninvasiveness of clinical stage IA lung cancer based on the findings of thin-section computed tomography (CT)[1], many thoracic surgeons have revealed that consolidation tumor ratio (CTR) and solid component size were more prognostic than maximum tumor size for resected non-small cell lung cancer (NCSLC)[2–6]. This finding is extremely important in the history of general thoracic surgery. Subsequently, the 8th edition of the TNM staging system drastically changed the staging system, with the clinical T category being determined according to solid component size and excluding ground-glass opacity (GGO)[7]. In contrast, new issues are emerging from the proposed changes concerning T parameters. Much of the confusion is caused by the absence of a consensus on how to make uniform the measurements of solid component size in many part-solid tumors in which solid component size is difficult or impossible to measure[8,9]. In such circumstances, we have reported a new and simple fact that the presence of a GGO denotes a great influence on the favorable prognosis of NSCLC, and the radiological solid component size is

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〔**Received Oct. 7, 2021**〕〔Accepted Nov. 1, 2021〕
J-STAGE Advance published date: Jan. 21, 2022

doi: 10.14789/jmj.JMJ21-0030-OT

irrelevant to the survival outcome of NSCLC if the tumors show a GGO component[10–17]. On the other hand, radiologically determined pure-solid lung cancers without a GGO component exhibit more malignant behavior and show several histologic types that have a poorer prognosis than do radiologically part-solid lung cancers. Thus, the prognostic impact of the solid tumor size is considered to be meaningful only in the pure-solid NSCLC[10–15]. This fact is extremely important when considering future revision of the clinical T staging and the proper operative strategies of lung cancer, provided that the clinicopathologic and oncologic outcomes are disparate between part-solid and pure-solid tumors on the basis of a GGO presence. In this report, we would like to demonstrate the latest clinical evidence regarding the small-sized lung cancer, and to discuss the appropriate operative modes based on these clinical evidences.

Latest clinical evidence of small-sized lung cancer

To date, there are numerous studies to evaluate the radiological and pathological correlation of early-stage NSCLC in Japan[18–20]. Based on the findings of thin-section CT scan, small-sized lung cancer is radiologically comprised of 2 parts, which is consolidation part and ground-glass opacity component[1]. Ground-glass opacity, or GGO is defined as an area of a slight, homogenous increase in density that do not obscure the underlying vascular marking (Figure 1). When the tumor is surrounded by a GGO component, it is called as part-solid tumor with a GGO. By contrast, pure-solid tumor is recognized as a tumor without any GGO component[12, 16, 21] (Figure 1). And it is well known that the ratio of consolidation part to the maximum tumor size well reflects the tumor aggressiveness in early-stage lung cancer[1]. When we defied a consolidation to tumor ratio (CTR), which indicates the ratio of maximum consolidation diameter to the maximum tumor diameter, tumor size less than 2cm and CTR less than 0.25 was defined as a radiologically non-invasive lung cancer to predict pathological non-invasiveness based on the result of JCOG0201 trial[1]. Furthermore, the 5-year survival outcome was significantly different when the cutoff point of CTR was selected as 0.5 (CTR≤0.5, radiological non-invasive; 96.7%, CTR>0.5, radiological invasive; 88.9%, $p<0.001$)[1, 22]. However, even in the radiological invasive lung cancer with a CTR more than 0.5, recent study shows that the presence of a GGO component has a strong impact on the favorable prognosis of lung cancer[10, 13, 17].

Until now, we focused on the clinicopathological and prognostic importance of a GGO component from several aspects. In general, we have reported that the lung cancer with a GGO component showed less invasive feature compared to the radiological pure-solid tumor. For instance, among patients with clinical-stage IA disease with a radiological invasive appearance (i.e., CTR>0.5), the

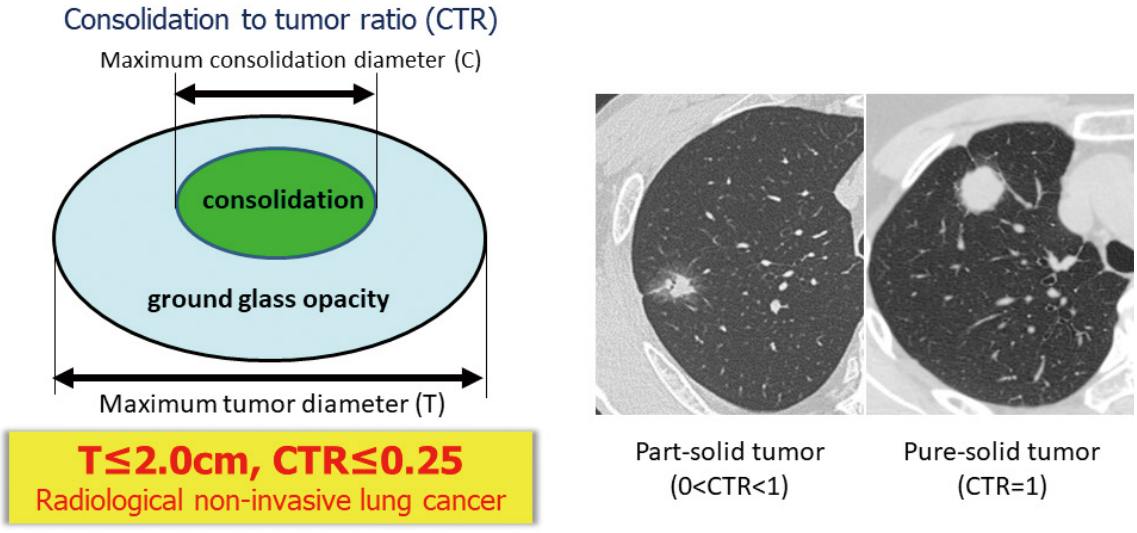


Figure 1 Definition of the consolidation to tumor ratio, and the typical findings of part-solid tumor and pure-solid tumor based on thin-section computed tomography[1].

frequency of pathological nodal metastasis is quite distinct based on the presence of GGO component, which is approximately estimated that the pathological nodal metastasis is found in 3–5% of part-solid lung cancer (0.5<CTR<1.0), but 15–20% of pure-solid lung cancer (CTR=1.0)[14]. Furthermore, among the c-stage IA radiological invasive lung cancer (CTR>0.5), the prognosis is significantly different between the part-solid tumor with GGO and the pure-solid tumor without GGO, and the survival differences were never shown in radiological invasive NSCLC with GGO component (0.5< CTR<1.0), which was regardless of solid component size or CTR[10, 13, 17]. All the more, the prognosis is quite excellent showing more than 90% in 5y overall survival (OS), if tumor has a GGO component[10–13, 15, 23, 24]. In contrast, radiologically determined pure-solid lung cancers without a GGO component exhibit more malignant behavior and show several histologic types that have a poorer prognosis than do radiologically part-solid lung cancers. Furthermore, as shown in our previous study (Figure 2), the prognostic impact of the tumor size is considered to be meaningful only in the pure-solid NSCLC[10–13, 15, 23, 24]. That is, the survival curves split almost fairly among the different solid component sizes only in radiological pure-solid lung cancer. This fact is extremely important when considering future revision of the clinical T staging of lung cancer, provided that the clinicopathologic and oncologic outcomes are disparate between part-solid and pure-solid tumors on the basis of a GGO presence.

Proposal for novel clinical T staging

Based on the latest clinical evidences, we are rigorously proposing a proper lung cancer staging for the next clinical T classification. Currently, solid component size is used as a clinical T factor based on the 8th edition of TNM staging system[7] (Figure 3). However, several issues are arising regarding the application of the solid component size as a clinical T staging. At first, inconsistency exists between radiological solid component size and pathological invasive size in part-solid lung adenocarcinomas, because the solid area often represents a benign scar or a fibrous scar harboring a stromal invasive component in part-solid tumors[25, 26]. Furthermore, there are several findings of part-solid tumors in which the solid component size is quite difficult or impossible to measure due to the presence of multiple, complicated or scattered solid areas rather than a single focus[8, 9, 27], which has not been absolutely determined in the new proposal. In the 8th edition of the T classification, there is no consensus

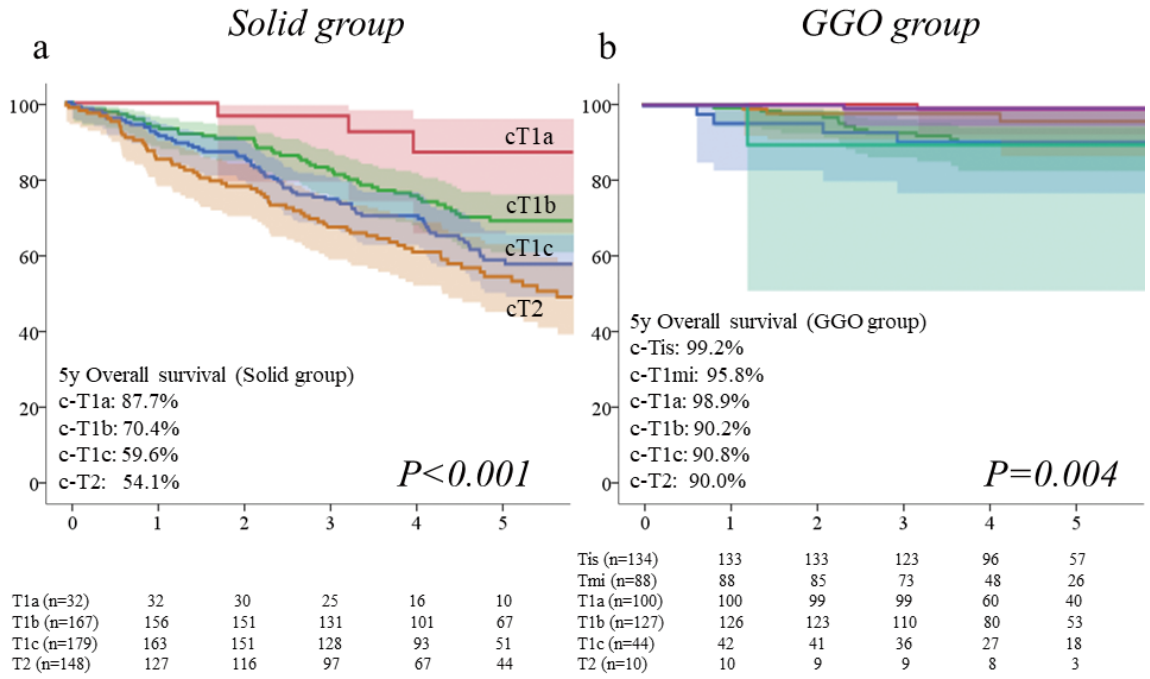


Figure 2 Clinical T category was compared in the GGO and Solid groups, respectively. The 5y-OS was excellent being 90% or more despite the revised T categories, provided the tumor had a GGO appearance. In contrast, maximum tumor size significantly separated the OS in the Solid arm (p<0.001)[12].

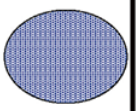
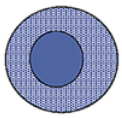
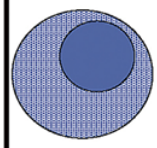
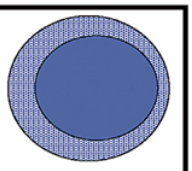
cT*	CT image on HRCT						
	Solid part	0 cm	0 cm	≤0.5 cm†	0.6-1.0 cm†	1.1-2.0 cm†	2.1-3.0 cm†
	Total tumor size including GG	≤0.5 cm	0.6-3.0 cm‡‡	≤3.0 cm‡‡	0..6-3.0 cm††	1.1-3.0 cm††	2.1-3.0 cm††
	Pathologic Differential Diagnosis	AAH‡, AIS, MIA	AIS, MIA, LPA	MIA, LPA, AIS	LPA, Invasive AD, MIA	LPA, Invasive AD	Invasive AD
	Clinical Stage*		cTis‡‡	cT1mi‡‡	cT1a	cT1b	cT1c
pT	Invasive part	0 cm	0 cm	≤0.5 cm‡‡	0.6-1.0 cm†	1.1-2.0 cm†	2.1-3.0 cm†
	Total tumor size including lepidic growth part	Usually ≤0.5 cm‡	≤3.0 cm‡‡	≤3.0 cm‡‡	0.6-3.0 cm††	1.1-3.0 cm††	2.1-3.0 cm††
	Pathology	AAH	AIS	MIA	Lepidic predominant AD or Invasive AD with lepidic compnent	Invasive AD with a lepidic component or lepidic predominant AD	Invasive AD with lepidic component
	Pathologic Stage		pTis‡‡	pT1mi‡‡	pT1a	pT1b	pT1c

Figure 3 Proposed 8th edition of the cT and pT descriptor classifications of small lung adenocarcinomas with a GGO and lepidic component by computed tomography and pathologic diagnosis[7].

on how to make uniform the measurements of solid component size in many part-solid tumors[7]. These include not only typical GGO-dominant or solid-dominant part-solid tumors including multifocal expression, but atypical part-solid lesions such as GGO with scattered consolidations[9] (Figure 4A and 4B), GGO with island shaped consolidations[28, 29] (Figure 4C and 4D), or GGO mimicking organizing pneumonia[27] (Figure 4E and 4F).

All the more, there exists more critical and fundamental issue in the classification of lung cancer staging. Based on the previous background, we always deem whether it is necessary to classify the prognosis of part-solid lung cancer with a GGO based on the solid component size. Again, clinicopathological and oncological features are significantly different between part-solid tumor with GGO and solid tumor without GGO. Therefore, we proposed to classify the current T staging to the subgroup based on the presence or absence of GGO (i.e., GGO group and Solid group). As a result, the 5y-OS was distinct in pure-solid tumor without GGO, which was worse based on the tumor size. However, the prognosis of part-solid tumor with a GGO component was not significantly different regardless of the solid component size, and their prognosis was excellent, which was irrespective of the current T staging[12] (Figure 2). This fact is extremely important when considering future revision of the clinical T staging of lung cancer, provided that the clinicopathologic and oncologic outcomes are disparate between part-solid and pure-solid tumors on the basis of a GGO presence.

Recently, this concept has been gradually noticed not only in Japan but several other countries[30-35]. Despite single institution advocacy for the prognostic importance of the presence of a GGO component as a significant clinical T parameter, however, this notion has not been fully confirmed across institutions or at a nationwide level. To validate this fundamental and simple prognostic feature of lung cancer, we aimed to demonstrate the prognostic impact of the presence of a GGO component in clinical stage IA NSCLC based on the long-term follow-up data of JCOG0201[15]. As a result, significant center validation also suggested the favorable prognostic impact of the presence of a GGO component in the prospective JCOG0201 dataset.

The principle behind the TNM staging system is the classification of cancers into groups according to the anatomic extent. This contributes to evaluate treatment strategies and to give some indica-

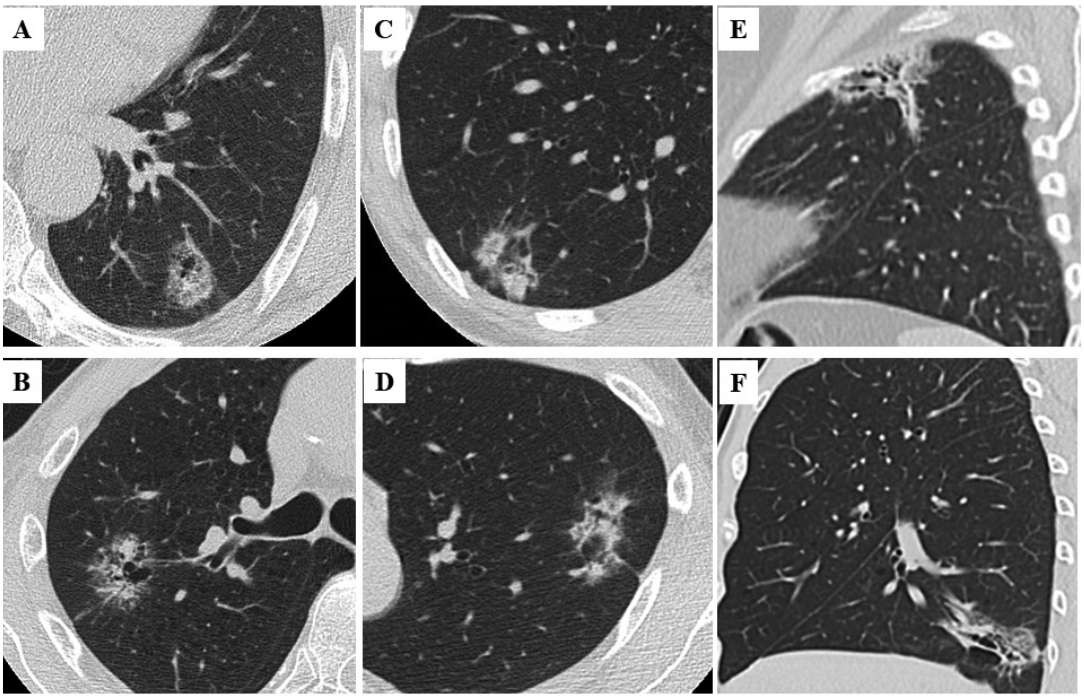


Figure 4 Radiological findings of part-solid lung adenocarcinomas with a solid component size that is difficult to measure: GGO with scattered consolidations (A, B), GGO with island shaped consolidations (C, D), or GGO mimicking organizing pneumonia (E, F).

tion of prognosis for survival. Hence, precise measurement of tumor size is crucial to improve stratification of lung cancer in the future. Based on these clinical backgrounds, we propose a new clinical T staging based on a GGO component in many reports, because we believe that the T staging should be simple, useful and reproducible to reflect the prognosis of lung cancer. Based on our clinical research, 5y-OS of part-solid lung cancer with GGO was more than 90% regardless of whole tumor size or solid component size. Therefore, we believe that part-solid lung cancer could be demonstrated as c-T1a despite their tumor size. In contrast, Tumor size has a great impact on the prognosis only in radiological pure-solid lung cancer. Therefore, tumor size effect should be exclusively applied to the radiological solid lung cancer without GGO component (Figure 5)[12, 36].

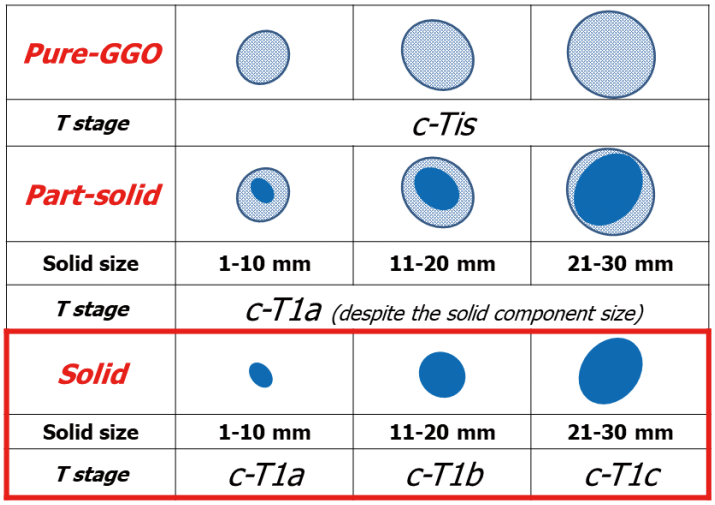


Figure 5 Proposed clinical T category based on the presence of a GGO component[11, 36].

Appropriate operative strategy for small-sized lung cancers

Today, standard operative mode for resectable lung cancer is recognized as lobectomy, this is based on the evidence from USA in 1995[37]. This randomized trial evaluated the OS of lobectomy and limited resection for clinical T1 non-small cell lung cancer. As shown in the report by Lung Cancer Study Group, lobectomy conferred limited or sublobar resection in both overall survival and recurrence-free survival (RFS). And the rate of locoregional recurrence of limited resection was 3-times higher than lobectomy. Hence, it is considered that the great caution is needed to indicate the limited pulmonary resection for lung cancer. However, due to the advancement of thin-section CT scan, more and more small-sized lung cancer was detected. Furthermore, based on the radiological and pathological correlations, we can predict pathologically less invasive tumor based on the radiological features. Currently, one of the most important prognostic factors would be a presence or absence of a GGO component, as presented in this lecture. Hence, it is possible to change the paradigm of standard operative strategy in a future[16].

Here, I would like to introduce 2 important trials conducted in Japan. These studies have been performed by JCOG lung cancer study group. The first trial presents a phase II study to evaluate the feasibility of wide wedge resection for GGO-dominant lung cancer, JCOG0804 trial[38]. The second trial present a phase III study to evaluate the survival outcomes between segmentectomy and lobectomy for radiologically invasive lung cancer[39]. At first, with regard to the feasibility study to evaluate the wedge resection for GGO-dominant or less invasive lung cancer, the 5y-RFS was 99.7%, which was quite excellent result[38]. Hence, it is considered that the sublobar resection, preferably wedge resection, is enough for GGO-dominant lung cancer. Furthermore, the result of survival outcome for radiologically invasive lung cancer will be disclosed near future. We should carefully await this randomized trial of segmentectomy compared to lobectomy in radiologically invasive small-sized lung cancer to consider the appropriate operative modes of small-sized peripherally located NSCLC. However, at the standpoint of tumor invasiveness, there exist several controversies regarding the appropriate operative strategy for radiological invasive lung cancer. In particular, as introduced in many times in this lecture, radiological pure-solid lung cancer without GGO component shows aggressive invasive nature, and we have reported the higher frequencies of locoregional recurrence after segmentectomy for clinical-stage IA radiological pure-solid lung cancer[40, 41]. With regard to the proper operative modes for peripherally located small-sized lung cancer, the result of randomized trial of segmentectomy compared to lobectomy is awaited, however the indication of segmentectomy or limited surgical resection for radiological pure-solid tumor should be in great caution from the point of cancer control.

Conclusions

In this lecture, we demonstrated the latest clinical evidence and the operative strategies for small-sized lung cancers. In early-stage lung cancer, it has been clarified that the presence of a GGO is strongly contributed to the oncological aggressiveness and prognosis. This indicates that not a solid component, but a presence of GGO in itself is a matter of concern regarding the prognosis of small-sized lung cancers. Based on the clinical evidences, lung adenocarcinoma with a GGO component is deemed as a favorable clinicopathologic subgroup different from the pure-solid tumor. Clinical T staging should be classified based on the presence of a GGO, and tumor size be applied only to the radiological solid tumor. With regard to the operative strategies for small-sized lung cancer, it is awaited the result of randomized trial of segmentectomy compared to lobectomy in radiologically invasive small-sized lung cancer, however, it should be fully deliberate regarding the indication of limited surgical resection for radiological pure-solid tumor.

Acknowledgments

Not applicable.

Funding

This work was supported in part by a Grant-in-Aid for Cancer Research from the Ministry of Health, Labour and Welfare, Japan, the Smoking Research Foundation, and the National Cancer Center Research and Development Fund (26-A-4).

Author contributions

AH performed the manuscript conceptualization, data curation, formal analysis, investigation, and writing of the original draft. KS contributed to the manuscript conceptualization, supervision and review & editing of the original graft.

Conflicts of interest statement

We have no conflict of interest to disclose.

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Publication List

Juntendo Medical Journal
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Gastroenterology and Minimally Invasive Surgery

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An asterisk (*) denotes doctoral works by Japanese students.
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Breast and Endocrine Surgery

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Cardiovascular Surgery

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General Thoracic Surgery

〈Original Articles〉

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Pediatric General and Urogenital Surgery

〈Original Articles〉

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Transfusion Medicine & Stem Cell Regulation

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Orthopedics and Motor Organ

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Plastic and Reconstructive Surgery

〈Original Articles〉

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(Updated: May 27, 2021)

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JUNTENDO MEDICAL JOURNAL
Vol. 68 No. 1 (936th issue)
Published on February 28, 2022
First published in 1875

Published by The Juntendo Medical Society
2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan
TEL: 03-5802-1586 E-mail: j-igaku@juntendo.ac.jp

Printed by Koryosha Co. Ltd.
4F, 2-31-25 Yushima, Bunkyo-ku, Tokyo 113-0034, Japan
TEL: 03-3868-3352 E-mail: jmj@koryo-co.com

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編 集 後 記

世界の偉人ランキングで常に上位であるナイチンゲールだが、彼女は近代看護の創始者と認識されている。その理由は看護行為を科学的なアプローチにより定義し説明し、そして実践を行い、看護行為が患者の回復に大きく寄与することを証明し、更に病気の快復のみならず健康の維持と疾病予防に大きく寄与したからである。ナイチンゲールは90歳（当時にしては非常に長寿だが、ブルセラ病で37歳以降はベッドでの著作が活動の主であった）で亡くなるまで多大な著作・文献を残した。特に有名なのはクリミア戦争中の兵士の高死亡率の劇的な改善である。その原因が病院での感染症によるものであることを、統計学を駆使したダイヤグラム（ナイチンゲールが開発）を用いて上層部に提示した。その結果、政府は病院の建築構造の改築を行い、換気・排水・暖房は改善された。更に看護により清潔や栄養が保持され兵士の死亡率は大幅に低下し、ナイチンゲールは英国の英雄となった。ナイチンゲールがその当時（日本ではペリーによる黒船来航時）主張した物理的・精神的・社会的な環境改善が今の新型コロナウイルスへの予防や対応に見事に当てはまると、多くの識者が指摘しているのは納得のいくところである。

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櫻井しのぶ
医療看護学部・公衆衛生看護学講座

イラスト作者より

コロナ感染拡大が続き、今はとうてい望めませんが、海外旅行が趣味の友人が数年前に訪れたペルーの人形を持ってきてくれました。早速、教室のレッスンにモチーフとして使うことにしました。エキゾチックな顔立ちと民族衣装です。（宮道明子）

順天堂醫事雑誌の記事については既に明治8年の創刊号から電子化されており，J-STAGE（科学技術情報発信・流通総合システム）の電子ジャーナル公開システムにおいて閲覧することができます．順天堂医学会のホームページからもご覧いただけますので，ご活用頂ければ幸いです（https://www.juntendo.ac.jp/journal/）．

特集の企画募集

「順天堂醫事雑誌」では，医学界の最新知識を紹介するために，特集として総説を毎号に掲載しています．
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順天堂醫事雑誌
JUNTENDO MEDICAL JOURNAL
第68巻　第1号（通刊936）
令和4年（2022年）2月28日発行
明治8年（1875年）創刊

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発行責任者　長　岡　　功
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〒113-0034　東京都文京区湯島2-31-25-4F
電話 03-3868-3352　E-mail: jmj@koryo-co.com

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抄　録

Juntendo Medical Journal
2022. 68(1), 92

精神疾患ゲノミクスの進歩

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双極性障害や統合失調症などの精神障害は高い遺伝力をもつことが知られている。遺伝因子の精神障害への寄与は確かであるが、ある疾患に対する遺伝的要因の特定は長い間謎であった。ヒトゲノム計画の報告により、「ゲノミクス」と呼ばれるヒトゲノムの包括的な分析が可能となった。ヒトゲノム計画に続くゲノム技術の開発によって、さまざまな病気に関連する遺伝情報を解明し、病態理解を深めることができるようになった。精神障害に関するゲノム研究も例外ではない。このレビューでは、特に我々の行ってきた双極性障害ゲノム研究に焦点を当て、精神医学ゲノミクスの近年の重要な進歩を紹介する。国際コンソーシアムとアドボカシーグループによって精神医学ゲノミクスが加速されており、サンプルサイズと検定力が高まることでより確かな知見が提供されている。統合失調症の遺伝的構造は、コモンバリアント研究とレアバリアント研究の両方で解明されつつある。自閉スペクトラム症の遺伝的構造は、主にレアバリアント分析によって解明されてきている。双極性障害に関しては、コモンバリアント分析がレアバリアント分析に先行しているものの、我々は疾患に関連するレアバリアントを解明するのに努めている。ゲノミクスのアプローチにより、特定の精神障害の遺伝的要因を説明できるようになったが、疾患間で重複するリスク遺伝子・多面発現が予想以上に観察されている。ゲノム解析により、精神障害の現在の分類体系の境界は多かれ少なかれ再考が必要とされていると言える。遺伝子型と表現型の関係をより深く理解するために、"genotype-first" アプローチと呼ばれる、遺伝子型に基づいて表現型を理解する試みが開始されてきている。最後に、精神障害のより良い理解と治療に向けたこの新しいアプローチについて議論したい。

キーワード： genomics, psychiatric disorder, bipolar disorder, schizophrenia, autism spectrum disorder（ASD）

この抄録は，順天堂醫事雑誌 68 巻 1 号，p2-11，2022 掲載の『The Current Progress of Psychiatric Genomics』の和文抄録です.

抄　録

Juntendo Medical Journal
2022. 68(1), 93

メラトニンおよびオレキシン神経伝達を介したせん妄予防

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せん妄の基本的概念は覚醒度の障害である．それに加えて，不眠，過剰な午睡，概日リズムの混乱を含む睡眠覚醒サイクル障害が特徴的な臨床像として示されてきた．それに対して非薬物的介入はある程度の成果を収めたが，せん妄が種々の生物学的機序をもつためその効果には限界がある．薬物的介入のうち抗精神病薬は有効のようであるが，錐体外路症状のような副作用が比較的高頻度で出現することから予防的投与には適さない．近年，新たな不眠症治療薬がせん妄予防に関して注目を浴びている．最近のメタ解析によって，メラトニン受容体作動薬やオレキシン受容体拮抗薬はせん妄予防に有効であることが示され，リアルワールドデータによってそれらは支持されている．

キーワード：せん妄，メラトニン，オレキシン，予防，睡眠覚醒サイクル障害

この抄録は，順天堂醫事雑誌 68 巻 1 号，p12–16，2022 掲載の『Prevention of Delirium Via Melatonin and Orexin Neurotransmission』の和文抄録です．

順天堂医学会 会員の皆様

順 天 堂 医 学 会
会長　服部　信孝

順天堂医学会短期海外留学時助成金給付制度

順天堂医学会では短期海外留学時助成金給付制度を開始いたしました。

1. 要件

下記すべての要件を満たす者

(1) 順天堂大学（大学院を含む）の学生で 1 か月以上 12 か月未満の海外留学をする者
(2) 留学先の研究機関または財団などからの援助がない者
(3) 医学会の正会員として 1 年以上の経歴を有し、医学会費を完納している者

2. 申請書類

(1) 順天堂医学会短期海外留学時助成金申込書
(2) 所属長の推薦書
(3) 申請者の主な研究テーマ・研究業績
(4) 留学受け入れ機関の指導者からの推薦状

3. 助成金の給付金額

留学期間	助成金額
1 か月以上 4 か月未満	10 万円
4 か月以上 7 か月未満	20 万円
7 か月以上 12 か月未満	30 万円

4. 申請スケジュール（年 2 回）

申請期限	助成決定時期
6 月末	8 月
12 月末	2 月

5. 選考機関：順天堂医学会短期海外留学時助成金選考委員会

6. 助成後の義務

(1) 帰国後直近の順天堂医学会学術集会において研究成果の発表および、その内容を「順天堂醫事雑誌」に報告する。
(2) 帰国後は、順天堂大学またはその関連機関に原則として 3 年以上勤務する。

7. 本件の照会先

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