Respiratory medicine

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Control of breathing

The relation between neural reflexes in the upper airways and control of breathing has been studied by Nishimura et al. [1]. They first showed that switching from nasal to oral breathing is reflexly controlled by sensory receptors located in the nasal mucosa [1]. Secondly, they demonstrated a close linkage between swallowing motion and control of breathing. Thirdly, they found that nasal continuous positive airway pressure (CPAP) suppresses the frequency and initiation of the swallowing motion, suggesting possible aspiration pneumonia during nasal CPAP.

Genetic factors in the control of breathing have been studied by Nishimura et al. [2]. A longitudinal study in normal subjects demonstrated that the hypoxic, but not the hypercapnic, ventilatory response is well preserved in terms of inter-

individual variation for 10 years [2]. A depression due to ageing was shown in this study for the hypoxic, but not the hypercapnic, response. A stronger genetic influence on hypoxic chemosensitivity was also demonstrated in adult twins by Kobayashi et al. [3].

Mechanisms for ventilatory depression after initial ventilatory stimulation during sustained hypoxia were extensively studied with respect to cerebral blood flow [4], endogenous adenosine [5] and upper airway muscle [6].

The mechanisms of dyspnoea are largely unknown. The roles of lung volume [7],afferent neural pathways [8], respiratory muscle fatigue [9], endogenous opioids [10] and personality [11] were examined.

Airway epithelium, glands and smooth muscle

Munakata et al. [12], developed a liquid circulating system to investigate airway and epithelial functions in vitro. They found a protective effect of airway epithelium against some constricting agents administered from the luminal side [12], possible involvement of epithelium-derived relaxing factor and exclusion of NO from this mechanism [13].

Shimura et al. [14] found, by separating single
submucosal glands from the animal airway, a squeezing of fluid by the myoepithelium and a significant influence of inflammatory mediators and drugs on submucosal glands.

Ebina et al. [15] studied the relation between airway diameter and airway smooth muscle thickness. The proportion of smooth muscle was largest in the terminal bronchiole, suggesting an important role of this particular portion for controlling airflow. They also found, from lungs removed post mortem, that asthmatic patients may be classified into two types: a group with smooth muscle hyperplasia, which is largely found in the large airways, and a group with hyperplasia, which is seen throughout large and small airways.

Gene structures from thromboxane A\(_2\) [16], platelet-activating factor [17] and endothelin were clarified in Japan [18].

**Pulmonary emphysema and bronchiolitis**

Pulmonary emphysema associated with \(\alpha\)-antitrypsin deficiency is extremely rare in Japan. A new variant of the deficiency found in patients from the Siiyama district had mutation of Ser-53 (TCC) to Phe-53 (TTC) [19]. This variant form is found in about half of the 12 Japanese families with the deficiency.

Diffuse pan-bronchiolitis is believed to be exclusively found in Asians. An HLA analysis of this unique disease revealed a high occurrence rate of the Bw52 locus (63 versus 11\%) [20]. This particular locus is found exclusively in Asians, not in Caucasians, Blacks or Hispanics.

**Interstitial pneumonia of unknown cause**

Homma et al. [21] found a more frequent history of 'dust' inhalation among patients with idiopathic interstitial pneumonia (IIP). They also found an IIP-like X-ray shadow in 1.3\% of the 1952 miners [21]. Post-mortem IIP lung specimens contained more silica and aluminum per unit of lung weight. From these facts, they believe that dust inhalation is important for triggering the inflammatory process in IIP.

Other groups found evidence of viral infection as a possible trigger of IIP. Ueda et al. [22] reported a high prevalence of hepatitis C virus antibody among patients with IIP. Sugimoto et al. [23] demonstrated a strong association of HTLV-1 myelopathy and T-lymphocyte alveolitis. Furthermore, proliferation of alveolar T-lymphocytes is associated with HTLV-1-infected cells.

Kuroki et al. [24] found a unique elevation of a pulmonary surfactant protein in the sera of patients with IIP. This elevation is accompanied by decreased phosphatidylglycerol in bronchoalveolar lavage fluid.

**Pulmonary oedema and pulmonary thromboembolism**

Patients with a past history of high-altitude pulmonary oedema have augmented pulmonary arterial pressor responses to hypoxia, low ambient pressure and exercise. These patients also showed increased atrial natriuretic peptide secretion after 10% \(\text{O}_2\) inhalation [25]. These results may indicate a 'predisposition' to pulmonary oedema through an abnormal pressor response in the pulmonary artery.

Takekawa et al. [26] found a transient rise in the serum IgE concentration in acute-phase pulmonary thromboembolism associated with infarction and pleural fluid accumulation. This finding may be important for the diagnosis and pathogenesis of the life-threatening disease.

**Granulomatous lung disease**

Summer-type hypersensitivity pneumonitis is mostly seen in the western part of Japan. Ando et al. [27] identified *Trichosporon cutaneum* as a causal agent for this disease through identification of serum antibody and inhalation challenge. An elevation in the level of CD8 cells is characteristic of summer-type hypersensitivity pneumonitis, whereas it is decreased in farmer's lung disease, another type of hypersensitivity pneumonitis predominantly found in the eastern part of Japan [28]. The mechanisms of these contrasting phenomena are worth studying. Smoking is known to depress the initiating mechanism of the disease and the serum antibody concentration to moulds is decreased in smokers. Yamaguchi et al. [29, 30] found decreased production of interleukin-1 and tumour necrosis factor by alveolar macrophages of smokers.

Kunikane et al. [31] reported a high occurrence rate of HLA DRw52 antigen in patients with sarcoidosis. This finding was confirmed by other groups in Japan and Germany. Although a specific antigen identified serologically is apparently related to 'disease sensitivity', DNA-level typing should be explored in future studies.

**Lung cancer**

Cellular and molecular aspects of primary lung cancer are recent research topics in Japan.

Cytochrome P450-IA1 gene polymorphism (classified into A, B and C) and lung cancer risk were studied by Nakachi et al. [32]. The risk for type C individuals is three times greater than that for those of type A and the former type is assumed to have lung cancer with 30\% less smoking than types A and B.

Kobayashi et al. [33] found a point mutation of the K-ras codon 12 in 15\% of patients with adenocarcinoma and those patients have larger and highly differentiated tumours. Harada et al. [34] examined surgically resected specimens from patients with non-small-cell cancer to determine the importance
of ras-p21 expression. A longer tumour size and shorter survival time were found in the ras-p21-positive group. Among many cancer-suppressing genes, abnormal p53 expression was found in 75% of small-cell cancer and 45% of non-small-cell cancer. P53 expression was demonstrated in early stages of non-small-cell cancer (T1 and N0) by Sameshima et al. [35]. Abnormal p53 expression in the primary tumour is well-preserved in metastatic tumours and, inversely, if abnormal p53 is not found in the primary tumour, it is rarely demonstrated in metastatic tumours. However, no relation was found between clinical stage as demonstrated by tumour, node and metastasis classification and p53 abnormality. From these observations, abnormal p53 seems to be expressed even in the early stage of tumour formation.

A larger DNA content of small-cell cancer indicates a higher sensitivity to chemotherapy but it is not necessarily related to good prognosis [36]. As for non-small-cell cancer, Isobe and associates observed a progressive increase in DNA content (flow cytometry) as the clinical stage advanced [37]. Furthermore, patients with DNA aneuploidy had a poorer prognosis in squamous cell carcinoma but not in adenocarcinoma. DNA content and ras-p21 expression were independent prognostic factors in the study of Miyamoto et al. [38].

An adhesion molecule, cadherin, was discovered by Takeichi [39]. When E-type cadherin cDNA was introduced into L cells that had no cadherin activity, expression of induced cadherin was accompanied by intercellular adhesion.

Nucleolar activity of cancer cells can be expressed as a silver-staining nucleolar organizer region (AgNOR). Ogura et al. [40] found a high inverse correlation between tumour-doubling time demonstrated by chest X-ray films and AgNOR spots in adenocarcinoma as well as squamous cell carcinoma. Squamous metastasis cells had more AgNOR spots than normal bronchial epithelial cells but fewer AgNOR spots than carcinoma in situ [41].

References


Neurology

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Recent progress in the study of neurological diseases in Japan has been comprehensive and extensive. In this article, however, eight topics among many are reviewed.

Unique leukoencephalopathies with skeleto-dermatopathy

Two types of hereditary (autosomal-recessive) leukoencephalopathy unique to this region have been reported during the last two decades. One is 'membranous lipodystrophy', first described by Nasu et al. in 1973, which is clinically characterized by the onset of pain and pathological fractures in the extremities and progressive mental and intellectual deterioration. Recently, computed tomography or magnetic resonance imaging (MRI) has revealed atrophy or demyelination of the cerebral white matter and severe arteriosclerosis on post mortem. The clinical characteristics are predominant in males, pyramidal-extra-pyramidal symptoms, pseudobulbar palsy, intellectual and mental impairments, and lack of vascular risk factors. Six cases showed demyelination with sparing of U-fibres, multiple small foci of peri-vascular softening in the cerebral white matter and severe arteriosclerosis on post mortem.

Neural mechanism of reading and writing in the Japanese language

The written Japanese language is unusual in having two distinct sets of characters, kanji and kana. Recently, neuropsychological studies have revealed that the processing of kanji and kana involves different intrahemispheric mechanisms. Lesions to the inferior temporal lobe have been shown to lead to alexia and agraphia specific to kanji [4]. Lesions of the left parietal lobe can produce selective agraphia for kana [5] and Japanese deep dyslexic subjects have been found to be able to read kanji, but not kana [6]. A patient with left unilateral agraphia for kanji without apraxia having a lesion of the posterior body of the corpus callosum was reported [7], illustrating the possibility that there are different interhemispheric pathways for these two writing systems.

Multiple sclerosis (MS)

MRI of the brain and spinal cord has proven to be the most sensitive method for detecting the asymptomatic demyelinated lesions of MS [8]. The combination of Gd-DTPA and T2-weighted MRIs could distinguish between oedema and demyelinated lesions, and was much more sensitive than clinical examination in detecting disease activities [9]. Unmasking subclinical demyelinated lesions by intravenous administration of lidocaine should be useful also [10]. The usefulness of multimodal evoked potentials (MEPs) for detecting the lesions was assessed, and at least one of the MEPs was abnormal in 80% of the patients with clinically definite MS [11].

Nationwide survey of spinocerebellar degeneration (SCD)

A nationwide survey was performed during the period 1988 to 1991 by the Research Committee on Spinocerebellar Degeneration of The Japanese Ministry of Welfare and Health [12]. It consisted of three parts. The first postal survey estimated that the total number of patients with SCD in Japan was 5050 and the prevalence was 4.53 in 100,000. The second survey clarified the neurological and functional status of patients with SCD and showed a higher proportion of non-hereditary types of SCD in Japan, which is in contrast to a study in Europe, where hereditary SCD is predominant. The third,