Pick’s disease has been relabeled recently as frontotemporal dementia (FTD) and the epynymic term restricted to the autopsy finding of typical inclusion bodies. Frontotemporal dementia is being used as a technical term in journals, while relatives of patients, the lay public, and many practitioners find Pick’s disease (PiD), similar to Alzheimer’s disease (AD), more acceptable. Furthermore, FTD commonly denotes the behavioral disorder, hindering the aphasic and extrapyramidal manifestations from being recognized as part of the syndrome. Recent advances in histochemistry suggest further fractionation, but the discovery of chromosome 17 localization of the familial forms of the disease suggests the cohesiveness of the clinical and biological entity.

PiD: A CLINICAL OR PATHOLOGICAL ENTITY?

Arnold Pick described progressive aphasia and personality changes as the major clinical syndromes of frontotemporal atrophy more than 100 years ago. Subsequent focusing on round argyrophilic neuronal inclusions (Pick bodies) resulted in a confusing dichotomy over the term Pick’s disease. When used as a clinical entity, it refers commonly to a protean frontotemporal syndrome that may present in various combinations of a behavioral disorder and a progressive language deficit, as described by Pick and others. When used as a restricted pathological entity of typical inclusions, it is a relatively uncommon finding on autopsy. When the pathological picture lacks Pick bodies or has other distinguishing features, the relationship to PiD is not recognized or denied, even though the clinical picture is the same. Frontotemporal dementia is increasingly used instead of PiD, but the term lacks historical continuity or anatomical accuracy. A possible solution to this impasse is the proposed term “Pick complex” to cover a family of related conditions, of which Pick body dementia (PBD) is but one of the components. The varieties constituting the Pick complex share common clinical patterns and a wide range of histological patterns, but maintain unique features. A glossary of the clinical and pathological terms used to describe Pick complex appears in the Table.

BEHAVIORAL, APHASIC, AND EXTRAPYRAMIDAL PRESENTATIONS OFTEN MERGE

Frontal lobe dementia (FLD), characterized by apathy and social disinhibition was recently described as a distinct “if not new” entity. It was subsequently renamed FTD and more recently, frontotemporal lobar degeneration. The atrophy, which can be demonstrated on neuroimaging, often involves the temporal lobes. Some of the symptoms, such as hyperorality and hypersexuality, are also seen with bilateral temporal lesions (usually herpes encephalitis) in human and in animal experiments (the Kluver-Bucy syndrome). In addition to the characteristic personality and behavioral changes, there is relative preservation of episodic memory and visuospatial function. Extensive subcortical vascular disease of the frontal lobes may enter the differential diagnosis.
Although a language loss progressing to mutism is also included in the syndrome of FTD,\textsuperscript{2,4} progressive aphasia may appear as the first symptom and dominates the picture for several years without other cognitive deficits. A series of these patients characterized with decreasing speech output were described,\textsuperscript{7} and subsequently the condition was called “primary progressive aphasia” (PPA). Initially this was also conceived to be a unique entity, but the clinical and pathological overlap with frontotemporal atrophies and PiD was later emphasized.\textsuperscript{6} A fluent variety of progressive aphasia has been described as “semantic dementia,” in which patients lose semantic memory and the meaning of words but retain articulation and syntax. Patients with this condition who underwent postmortem examination also had the pathological features of Pick complex. Although many PPA cases progress slowly, many will develop the characteristic behavioral and personality alterations of FLD if they are followed up long enough. Both may develop CBD as well.

**Corticobasal Degeneration is Part of the Pick Complex**

First described as corticodentatonigral degeneration, this condition was later renamed corticobasal degeneration (CBD) and cortical basal ganglionic degeneration.\textsuperscript{7} The original description, and almost all subsequent ones, suggested a relationship to PiD. Extrapyramidal and subcortical involvement in PiD was well known before this. Clinical cases of CBD, defined as demonstrating unilateral rigidity, apraxia, and “alien hand,” have been described with typical Pick bodies and the pathological variant of CBD is often associated with FLD or PPA. In this sense, CBD is also dichotomous because the clinical CBD syndrome (CBDS) does not necessarily have CBD pathological features, and vice versa. Recently, vertical gaze palsy has been described increasingly in CBD, and this condition may be difficult to distinguish clinically from progressive supranuclear palsy. Even the pathological findings overlap to some extent. The nosological relatedness of these conditions awaits further clarification.

**Motor Neuron Disease (MND) is at Times Associated with FTD and PiD**

Although MND was described in association with PiD and Creutzfeldt-Jakob disease (CJD) many years ago, subsequently dementia with MND was considered a new entity.\textsuperscript{8} The association of FLD and PPA with MND was later recognized, identifying the dementia as FTD with MND. It appears that older descriptions of spongiform dementia with MND probably had a Pick-variant pathological picture rather than true CJD. Since protease-resistant prion proteins are used to define CJD, the differentiation of spongiform encephalopathies is placed on firmer scientific grounds. Furthermore, ubiquitin-positive, tau-negative inclusions in the cortex and brainstem characterize some cases of MND with FTD.\textsuperscript{9} However, there are cases of FLD with these pathological characteristics without MND. Many of the patients with FTD or PPA with MND have a rapidly progressive course, with early death from dysphagia. Conversely, the progression in some of the patients with MND may preclude the documentation of dementia.

**Pathological Substrata of Pick Complex**

The pathological substrata of Pick complex include PBD, CBD, dementia with ubiquitin-specific inclusions (USI) (MND-type dementia), basophilic inclusion body disease, and dementia lacking distinctive histopathology (DLDH). Pick body dementia, equivalent to “classic” PiD disease, or PiD type A of Constantinidis, is characterized by the presence of argyrophilic (but Gallyas-negative) round inclusions in the dentate gyrus, and other cortical and subcortical areas. The argyrophilic inclusions in the pathological entity of CBD adopt a variety of forms, including round Pick body–like, but unlike Pick bodies they do not involve the dentate gyrus and are stained by the Gallyas method. Pick bodies and the CBD inclusions contain aberrantly phosphorylated tau proteins, each demonstrating a distinct pattern on Western blots.\textsuperscript{10} The other entities do not possess neuronal inclusions associated with abnormal tau proteins. Ubiquitin-specific inclusions is the term we propose to designate the characteristic inclusions, invisible on ordinary stains, found in the dentate gyrus and the frontal cortex in patients with MND and dementia. Most commonly, however, patients demonstrating these inclusions do not have MND, but FTD. Basophilic inclusion body disease is an uncommon entity, previously described as the generalized form of PiD.\textsuperscript{11} Dementia lacking distinctive histopathology, possibly the most common form of the Pick complex, may or may not demonstrate ballooned neurons and dispersed perikaryal tau immunoreactivity, but shares with the other forms prominent superficial linear spongiosis in the atrophic regions. A lobar pattern of atrophy is always present, but the specific regions affected vary as much between individuals as among forms.
HISTOPATHOLOGICAL FORMS LACK A DIRECT RELATIONSHIP TO CLINICAL SYNDROMES

This is the direct consequence of the variation mentioned earlier, since the clinical syndrome is determined by the areas involved rather than the histopathological characteristics. Thus, CBD can be manifested as CBDS, PPA, or FTD. In fact, the syndromes of PPA and FTD can be caused by any of the histopathological forms. Conversely, both MND and a complex motor syndrome similar if not identical to CBDS can be seen in PBD.

The term Pick complex provides an umbrella covering these closely related varieties characterized not only by a lobar, but also subcortical, pattern of atrophy. In addition to preserving historical continuity with the disease first described by Arnold Pick, it emphasizes the commonality of clinical presentations and pathological mechanisms. While advances in histochemistry contributed significantly to the understanding of Pick complex, classifications have often underemphasized the overlap.

GENETIC LINKAGE TO CHROMOSOME 17 OCCURS IN MOST FORMS OF FAMILIAL PICK COMPLEX

Frontotemporal dementia phenotype associated with several histopathological forms has been linked to chromosome 17q21-22 in several families.12 This is the chromosomal region for tau, the microtubular protein that is prominent in PBD and CBD. There is a tendency to describe each of the families with chromosome 17 linkage as unique clinically and pathologically, but the underlying theme is a behavioral disorder continuity with the disease first described by Arnold Pick, it emphasizes the commonality of clinical presentations and pathological mechanisms. While advances in histochemistry contributed significantly to the understanding of Pick complex, classifications have often underemphasized the overlap.

PICK COMPLEX IS A COMMON DEGENERATIVE DEMENTIA

Although other conditions, such as Lewy body dementia, were claimed to be second only to AD in incidence, epidemiological studies are lacking. Lewy body dementia may not be easily distinguishable from AD clinically, and “pure” Lewy body dementia without AD-related changes is relatively rare. The often quoted ratio of incidence of PiD to AD is 1:10. This ratio may be even lower if only PBD is counted or higher depending on the criteria used for inclusion. The initial estimates of the incidence of FLD were about 20% of degenerative dementias, even without including cases of PPA and CBD.2,3 However, because of the considerable overlap between the various phenotypes of the Pick complex, any case that is reported as FLD at one center may be described as PPA at another depending on the course of illness, the time the patient was seen, and the interest of the investigators. If the clinical cohesiveness of the entity is acknowledged and the overlap recognized, the overall incidence of Pick complex is likely to be 25% of the degenerative dementias, raising the ratio of PiD to AD to 1:4. The clinical significance of Pick complex and lobar atrophy has been diluted by the dogma that lobar degeneration can be caused by a variety of pathological conditions, such as AD and CJD. Although these cases undoubtedly exist, they are few in number. Some are representative of Pick complex pathological features combined with age-related changes, mainly neuritic plaques. Most of these concepts are subject to ongoing debate, but they represent a significant development in the study of degenerative dementia.

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