On aphasia due to atrophy of the cerebral convolutions. By Dr G. Mingazzini, Professor of Neuropathology at the Royal University of Rome. *Brain* 1914: 36; 493–524.

Giovanni Mingazzini (1859–1929) is not slow to point out that he, Arnold Pick and Jules Déjerine had each described independently, and at about the same time, cases of aphasia that, at autopsy, were attributable to atrophy of the relevant cortical convolutions and not stroke or tumour. Since these and subsequent reports were scanty, he proposes to describe in detail the case of Pio Marini, a gilder, studied in life and post mortem at the lunatic asylum in Rome. In 1907 Sr Marini became impulsive and showed difficulty in speaking and understanding what was said. He used paraphasic substitutions and managed his frustrations with threats and rage. The symptoms progressed without sudden change such that his relatives had him committed to the asylum early in 1909. Examination shows no physical abnormalities of significance but his speech is extremely limited and characterized by echolalia, perseveration or meaningless reciting of his name (as Marino Pio) or that of one ‘Don Antonio’ in reply to questions, and when reading more than a few words aloud, writing to dictation, copying or following commands. He repeats with greater accuracy and versatility. Dr Mingazzini considers him to have ‘signs of partial sensory aphasia, amnesia verborum, verbal paraphasia, paralexia and almost complete agraphia’. By late 1910, Pio Marini remains physically able but he cannot navigate his environment, use household objects and cutlery, or dress. And his verbal output and response to attempts at communication remain limited to ‘Don Antonio’: ‘word-blindness and agraphia are complete, and word deafness is almost complete…the slow progress of the symptoms of aphasia, the absence of strokes or any focal symptoms, together with ever-increasing dementia, led me to conclude that the patient was developing progressive atrophy of the cerebral convolutions…this diagnosis was confirmed by his death, which occurred on December 15, 1910’. At autopsy there is focal decrease in volume, to half that normally expected, of the first and second, and the pars orbitalis and triangularis of the third left frontal convolutions and with some loss also of the temporal lobe and the angular gyrus resulting in widening of the corresponding sulci. Similar but less-marked changes are seen in the right hemisphere (Figs 1 and 2). Dr Mingazzini proceeds to examine histologically and compare selected frontal and temporal gyri from the left and right hemispheres. Throughout, the nerve fibres are attenuated and survivors both dilated and broken. Those making up the transverse and tangential bundles are particularly affected; and these sites are also conspicuous for the loss of nerve cells in all their cortical layers (Fig. 3). Surviving neurons show intact nuclei and nucleoli but their cytoplasm is either filled with yellow granular material or has largely disappeared (Fig. 4). Especially affected is the pars opercularis of the third left frontal convolution. ‘There is not always a correspondence between the changes in the nerve-cells, and those which have taken place in the medullary fibres…in the pars opercularis of the left F3, the changes in the fibres are very great [whereas] those in the nerve-cells are relatively little noticeable. On the other hand, in the passage zone between the left F3 and the gyrus praecentralis, the nerve-cells present extremely noticeable alterations, while the medullary nerve-fibres, though certainly changed, are altered to a much slighter extent’. Glia are relatively unaffected although damaged axons are surrounded by clumps of somewhat chaotically arranged surviving myelin (Fig. 5). Although relatively spared by comparison with gyri much affected in the left hemisphere (Fig. 6), there is loss of tangential and transverse fibres with varicose swellings and altered nerve-cell cytoplasm especially in the passage zone and pars opercularis of the right F3, whereas in the nerve cells of the right T1 most of the cytoplasm has disappeared and only a few of the nerve cells are missing.

Now, Dr Mingazzini proceeds to an analysis of case studies already published. In each, the pattern is apparent of ‘a double set of phenomena, of which one belongs to speech and the other to the mental processes’. Leaving aside the doubtful examples of Ascher and Shaw (in which general paralysis of the insane and stroke seem more likely explanations), Bischoff (1899) had described a case in whom all aspects of speech except repetition were severely impaired in association with bilateral temporal atrophy: in Liepmann’s (1900) patient, frontal and temporal atrophy had manifested in life as severe sensory aphasia with automatic echolalia; two cases described by Marie and Leri (1904), also with progressive sensory aphasia, had dilation of the right and left occipital poles, respectively; Mills (not cited) described aphasia progressing over 30 years in which autopsy revealed predominantly left-sided focal temporal lobe atrophy; Edlich’s (1902) patient progressed to complete motor and sensory aphasia, and agraphia with alexia, with sensory apraxia and agonal dementia and pathological laughter and tears, autopsy revealing extensive frontal lobe atrophy.

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Returning to his own report from 1902, although onset appears to have been heralded by a small stroke, aphasia progressed thereafter to complete incomprehension and the ability only to utter ‘be, be, po, po, pa’; and the patient was apractic with inappropriate laughter and tears. In the context of generalized brain atrophy, selective nerve-cell loss and accumulation of pigment in cytoplasm of survivors selectively affected the pars opercularis of F3. The same emphasis on histological abnormalities of nerve cells focused on the pars opercularis of the left frontal and various temporal convolutions in individuals suffering progressive aphasia—approximating to transcortical or subcortical sensory aphasias—in life is evident in cases reported by Alzheimer (1897), Déjerine and Séreux (1897), Rosenfeld (no date), Varaguth (1900), Stransky (1903) and Franchesci (1908). Special attention must be given to the three cases described by Arnold Pick (1904): a woman of 58 showed progressive loss of memory and personal identification, later losing her way in familiar circumstances and displaying features of aphasia that eventually dominated the clinical picture; case 2 had many similar features but retained slavish copying and echolalia; Pick’s third patient had progressive paralysis and disordered eye movements with amnesia verborum; all three showed generalized brain atrophy but with selective loss of tissue in the left frontal and temporal gyri.

‘As a general conclusion, we find that [the early] aphasic disturbance... consists in an incapacity to comprehend the meaning of words... gradually the disturbance becomes

Fig. 1 Photograph of the left cerebral hemisphere. Note the serious atrophy of the pars opercularis of F3 and of the middle portion of T1. Source: Fig. 4 from p. 499.

Fig. 2 Photograph of the right cerebral hemisphere of the brain. Note the conspicuous atrophy of the pars opercularis of F3 and of the middle and posterior portion of T1. Source: Fig. 3 from p. 499.

Fig. 3 Section of the cortex of the left T1 (stained with haematoxylin-eosin, enlargement objective 4, ocular 2, Leitz). Note the disappearance of many nerve-cells of the different strata of the cortex; the nerve-cells, especially the pyramidal ones (p), have to some extent lost their characteristic shape, owing to the loss of a considerable portion of the cytoplasm. Source: Fig. 10 from p. 505.
more and more noticeable, and finally the patient becomes indifferent to all questions... with the progress of the disease... echolalia always assumes the automatic form... amnesia verborum later gives place to a progressive reduction in the command... and repeating of pronounced words... finally every effort of the patient to speak merely results in the utterance of one or two words... although many of the patients were illiterate... in rare cases, the power of reading and writing remained unimpaired throughout the course of the disease... parallel to the aphasic disturbances... the patients neglected their business, became less efficient... and their critical faculty became weakened... [they] wandered about aimlessly... and no longer knew how to dress themselves... this symptom-complex is always completed by exaggerated emotion which culminates in spasmodic laughter or tears...'. Age at onset is between 38 and 76 years, men and women are equally affected; the course is slow and progressive, its duration on average around 4 years. Although the pathology predominantly targets the left frontal and temporal lobes, and occasionally the posterior cortical poles, these changes may occur in association with more generalized atrophy of the entire cerebral cortex: 'the corresponding histological alteration resolves itself
principally into a primitive degeneration of the nerve-cells and medullated fibres of the grey matter of the cortex, and of the axis of the convolutions’. As for clinico-pathological correlations, Dr Mingazzini sides with Pick in concluding that the decrease in command of words indicates involvement of F3 rather than temporal lobe structures, whereas the word-deafness can be attributed to atrophy of T1 and T2; amnesia verborum cannot reliably be localized; echolalia reflects the survival of the oldest language skill in ontogeny and hence it emerges in the most advanced stages when all other speech components are corrupt; and apraxia is a consequence of frontal lobe atrophy. But having dutifully rehearsed this catalogue of topographical psychology, Dr Mingazzini distances himself from rigid attempts at localization by acknowledging the confounding effects of generalized loss of intelligence eventually affecting these cases and, especially, the secondary effects on speech of psychic blindness and visual agnosia present in some of the cases. More generally, it seems clear that aphasis abnormalities will occur with damage not confined to the ‘speech region’ and without the associated paralysis and alteration in tendon reflexes expected in stroke and other focal lesions. But if the regional dependence of specific speech defects is unclear, less ambiguous is the conclusion that this form of progressive aphasia is due to nerve-cell loss in the various affected parts.

Once again, Dr Mingazzini reassures himself in closing: ‘I succeeded in forming a correct judgement during life, basing my conclusions on the fact that the sensory amnesic and aphasic troubles had developed slowly, that notable disturbances in the motor power, of the limbs at least, were wholly absent, and finally, that the patellar and the superior tendon reflexes were equal on both sides’. His last word addresses the doctrine of speech localization and the differences between aphasia with atrophy of the cerebral convolutions and loss of speech in other forms of dementia: ‘it may be doubtful … whether the incapacity to understand the meaning of any question whatever is a sign of simple senile dementia…[but] even in the most advanced stages of this psychosis, the patients always understand a certain number of questions, and do not reply like an echo, much less do they lose all command of language to such an extent as scarcely to be able to use one or two words…even in the total wreck of the intellect, such as occurs in advanced senile dementia, loss of the memory of graphic symbols has never been observed’. Thus, although more concerned with the accuracy of his diagnosis during life than the nature of the disease process he has observed, Dr Mingazzini has sensed the nuances of cognitive defects that distinguish the various dementia syndromes now recognized and in which—following the initial tranche of single case studies linked to mutations of progranulin reported elsewhere and in Brain last year—the spectrum of clinical, neuropsychological, imaging, genetic and pathological features to be observed in large cohorts of patients is now amplified (pages 706, 721 and 732).

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