Asperger's syndrome with unusual cerebral pathology: Case report and literature review

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Summary

A case of Asperger's syndrome with unusual cerebral pathological changes is reported. A 22-year-old male had been having diagnostic Asperger's syndrome since the age of eight and had epilepsy during the past two years. Radiological studies revealed a focal intra-axial cortical and subcortical cerebral lesion with hyper-intensity and non-enhancing contrast in the left frontal lobe. Histological and immunohistochemical studies demonstrated that the lesion consisted of cortical laminar disorganization, neuronal dysmorphism and increased heterotopic neurons in sub-cortical white matter. To our knowledge, this is the first case of Asperger's syndrome with focal cerebral pathological abnormalities rather than mini-columnar changes and the gyral malformation reported in the literature.

Keywords: Asperger's syndrome, brain, neuropathology

1. Introduction

Asperger's syndrome is characterized by impaired social communication with normal language skills and intelligence. Although this syndrome is not uncommon in childhood, the information about its neuropathological changes is very much limited, which has been barring the understanding of the etiology and pathogenesis of this disorder. The neuropathological findings that have been so far reported are cerebral cortical mini-columnar abnormalities and gyral malformation in four patients (1,2). Our report documents a case of Asperger's syndrome with cerebral abnormalities different from the previously reported neuropathological changes.

2. Case report

2.1. Clinical history

A 22-year-old male with history of Asperger's syndrome presented with chronic epilepsy for the past two years. The diagnosis of Asperger's syndrome was made when the patient was eight years old. For the past two years, the patient also had been having superimposed episodes of unusual movements, staring spells and headaches. The neuroradiological examinations showed a focal lesion with hyper-intensity and non-enhancing contrast in the left frontal lobe, corresponding to Brodmann's cortical area 47 (Figure 1). Surgical excision was subsequently performed, and the specimen was sent for pathological evaluation.

2.2. Macroscopy and microscopy

The excised brain specimen was grossly examined after fixation in 10% buffered formalin. The tissue was then paraffin-embedded, and 4-μm-thick sections were cut for staining. Sections were stained with hematoxylin and eosin as well as the avidin-biotin-complex immunoperoxidase technique with antibodies against glial fibrillary acidic protein (GFAP), neuron specific enolase (NSE), synaptophysin and Ki67. The stained sections were reviewed by three neuropathologists.

The specimen was received as soft tan and gray tissue fragments without hemorrhage and necrosis. Microscopically, the cerebral cortex and subcortical white matter were identified. The cortex showed...
laminar disorganization and scattered dysmorphic neurons, more significant in cortical layers 3, 4, 5 and 6 (Figure 2A). There were scattered dysmorphic or enlarged neurons in the white matter, mostly located in the subcortical region. The number of neurons and glial cells of cortex and glial cells of white matter was within normal range. The glial cell composition was unremarkable. There was no inflammation, neoplasm or hemorrhage in the specimen. Immunohistochemical studies demonstrated that clusters of GFAP positive glial cells and neuropile were distributed in an irregular and random fashion (Figure 2B). NSE and synaptophysin stains highlighted scattered dysmorphic neurons located in the cortex and subcortical white matter (Figure 2C). The proliferative index indicated by Ki67 was close to zero.

3. Discussion

Asperger's syndrome is characterized by severe and sustained impairment in social interaction and odd or eccentric behaviors. The patient is often pre-occupied with complex thoughts. However, the patient usually has normal intelligence and adequate language skills in some aspects such as vocabulary and grammar. Clinical manifestation is pervasive. The diagnosis is usually made when the patient reaches school age.

Although this disorder is clinically chronic and significant, its neuropathological changes are barely known. The only reported pathological findings in the medical literature were alteration of total number and size of cerebral cortical mini-columns in two patients (1), macrogyria in one patient and polymicrogyria in another patient (2). Our case demonstrates another group of histopathological changes that can be classified as a cerebral developmental abnormality. The pathological changes in this case are morphologically similar to those found in focal cortical dysplasia and are
more severe than the pathological findings previously reported in Asperger's syndrome. Clinically, this patient developed epilepsy at an older age. Epilepsy is an essential manifestation in patients with focal cortical dysplasia. This phenotypic combination of Asperger's syndrome and epilepsy indicates that Asperger's syndrome and focal cortical dysplasia might share the same spectrum of developmental neuropathology. The lower end of this neuropathological spectrum such as changes of cerebral cortical mini-columns produces Asperger's syndrome without seizures, and the higher end of the spectrum like focal cortical dysplasia causes epilepsy, while the neuropathological abnormalities between these two extremes might clinically manifest as Asperger's syndrome with or without epilepsy. Our case initially had Asperger's syndrome at a younger age and developed superimposed seizures at a later age. It is possible that the current cerebral abnormalities progressed from mild neuropathological changes such as abnormal cortical mini-columns or others.

It is believed that the frontal cerebral cortex is involved in higher cognitive functions such as undertaking of initiatives and planning of future actions in humans. The structural alteration of this cortex in Asperger's syndrome exhibits disordered social interactions. Anatomical studies and association with teratogens strongly suggest that the developmental alteration of brain occurs after conception. Abnormal migration of embryonic cells during fetal development changes the final structure and pathways of the brain, which results in alterations in the neural circuits that control thoughts and behaviors. Several theories have been proposed, but none of them can provide a complete explanation for Asperger's syndrome. Koechlin and Hyafil believed that a process called "cognitive branching" might be the core function of the frontal cerebral cortex. Cognitive branching enables a person to maintain a previously running task in a pending status for subsequent retrieval and execution upon completion of the ongoing one. Many of our mental activities and behaviors require simultaneous engagement of multiple tasks, which suggests the frontal cerebral cortex may perform a "domain-general" function in these scheduling processes. Burgess et al. proposed that there is a "supervisory attentional gateway" (SAG) system in the frontal cerebral cortex of the human brain. The SAG system operates under unusual conditions to ensure optimal use of cognitive resources and overcome a potential impasse that would otherwise be experienced by the system. This mechanism is involved in optimizing performance in many situations, from exploration to switching of tasks, and attention or behavioral organization over long periods of time.

In conclusion, this is the first case of cerebral abnormalities other than abnormal cortical mini-columns and gyral formations in Asperger's syndrome reported in the literature. This case expands our pathological view into Asperger's syndrome. A larger number of cases are obviously needed to investigate neuropathogenesis of this syndrome as well as other cerebral developmental disorders.

References


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