Reassessing the Cause of Death in Clinical Research

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Abstract

The direct examination of brain tissue in people with autism and similar illnesses is made possible by post-mortem investigations. There have been a number of review publications that have concentrated on certain post-mortem anomalies, but none that have compiled all of the post-mortem literature. Here, we conduct a thorough evaluation of the data from post-mortem investigations into autism and other illnesses that exhibit autistic symptoms. A few strikingly consistent conclusions are apparent despite the literature's short number of research and tiny sample sizes. Although there are constant changes in minicolumn numbers and abnormal myelination, cortical layering is essentially unaffected. Transcriptomics frequently links dysfunctional metabolic, apoptotic, proliferation, and immunological processes. Non-coding RNA, abnormal epigenetic profiles, GABAergic, glutamatergic, and glial dysfunction are all implicated in the pathophysiology of autism in sufficient numbers of independent studies. Overall, the frontal cortex and cerebellum are most frequently affected, occasionally showing unique region-specific changes. The body of research on conditions including Fragile X, Rett syndrome, and copy number variants (CNVs) that predispose to autism is extremely thin and contradictory. It is necessary to do larger trials that are matched for gender, developmental stage, co-morbidities, and drug use.

Introduction

One in 100 kids have autism, a severe neurodevelopmental disease. Repetitive behaviours, difficulties with social cognition and communication, and hypersensitivity to outside stimuli are some of its hallmarks. Individuals exhibit a wide range of comorbidities in addition to these fundamental symptoms, such as seizures, attention-deficit/hyperactivity disorder (ADHD), and other cognitive deficits. Autism is still primarily an ubiquitous and heterogeneous illness that is diagnosed by examining a person's behaviour and developmental stage, and the severity of the symptoms that each patient presents varies. Autism (as described above), Asperger syndrome (as described above but milder and/or without communication difficulties), Pervasive Developmental Disorders-not otherwise specified (PDD-NOS), where distinctions between all three conditions have been abandoned, Rett syndrome, and rare genetic disorders presenting ASD related symptoms are all included under the umbrella term Autistic Spectrum Disorders (ASD) in Diagnostic and Statistical Manual 5 [1].

The F84 section of the International Classification of Diseases (ICD) also lists Rett syndrome and other recognised causes of ASDs. Here, we refer to all of those syndromes collectively as autism and related illnesses. Although there is still much to learn about the pathophysiology of autism, Numerous genetic and environmental variables significantly influence its beginning and progression [2]. Numerous genetic locations and alleles associated with autism have been linked to genetic mutation inherited accounts for over 40% of the risk for ASD data from various computational research combined imply that genetic changes in developmental processes are connected to High co-expression of ASD susceptibility genes demonstrates the prevalence of ASD [3]. more likely to occur during two separate developmental phases and affect the perinatal/postnatal cerebellar cortex as well as the second trimester frontal-somatomotor neocortex.

Additionally, a number of environmental influences that occur before birth are linked to a higher incidence of ASD, such as maternal stress reaction activation and toxicant exposure during pregnancy.Three groups can be used to categorise the known genetic causes of ASDs. First, about 5% of cases are caused by a single gene mutation, which includes Fragile X and Rett Syndrome. It is true that not all people with Fragile X or Rett Syndrome exhibit autistic symptoms. Around of males have autism, compared to of Fragile X females and 61% of Rett Syndrome females. Second, about 10% of cases of ASD are caused by significant genomic copy number variants (CNVs), like deletions and duplications of a specific gene region [4].

These comprise the human chromosomal regions 16p11.2, 22q11, 15q11–q13, 15q13.3 microdeletion, and 15q11–13 duplication deletions and duplications. Post-mortem research therefore serves as an important interface between the clinical presentation and the underlying molecular and cellular disease, complementing other approaches. Numerous narrative reviews describing various facets of the neuropathology of ASD have been published. These have concentrated on the effects of epigenetic and transcriptome research as well as GABAergic deficits, mitochondrial dysfunction, microglial impairments, and neuroanatomical changes. The nature of the numerous results in post-mortem research, including the genetic, epigenetic, and transcriptome patterns in ASD brains disclosed, have not yet been the subject of a thorough systematic review that describes and synthesises them. In this article, we thoroughly examine the data from postmortem ASD research. Unusual but crucially, we also include post-mortem data in conditions such Fragile X syndrome (FXS), Rett syndrome (RTT), 15q11-13 duplication, and DiGeorge syndrome, which are frequently associated with autism [5].

Discussion

The majority of the post-mortem data presented here were derived from a small number of research that focused on specific ASD brain characteristics; very few studies examined the other illnesses. Nevertheless, some speculative conclusions can be made, in part because it will take years to gather post-mortem data for other research that might refute them. There is no evidence to support the idea that ASD causes dysregulated layer formation in the cortical layering, however reductions in the number of minicolumns and abnormal myelination have frequently been recorded. The numbers, densities, and volumes of neurons given here are not sufficiently constant throughout the various regions of the brain studied to allow for a generalization [6].

Several transcriptome studies have shown abnormal gene expression in the ASD brains, suggesting that these genes may act as susceptibility genes for the disorder and offering early suggestions on potential molecular mechanisms that might be involved in the pathophysiology of ASDs. Further evidence for aberrant synaptic, metabolic, proliferative, apoptosis, and immunological pathways in the ASD brain comes from transcriptomic research.Long and short ncRNAs that target ASD-risk genes or genomic areas have frequently been found to have dysregulated expression patterns. Additionally, epigenetic markers of ASD samples were different from those of controls; nevertheless, bigger cohort studies are needed to confirm the type and degree of epigenetic changes in ASD [7].

Reductions in GABA receptors, GAD levels in the cerebellum, reductions in RELN and PV, and altered levels of particular IN subpopulations are among the GABAergic abnormalities that are routinely

associated with ASD. Even though the imbalance between the excitatory and inhibitory systems (E/I) is a well-established notion for the pathophysiology of ASD, few studies have looked into the glutamatergic deficits, with the most consistent finding being an increase in glutamate receptors and transporters. Additionally, dystrophic characteristics and an increase in 5-HT neuron counts were regularly noted, suggesting a possible serotonergic malfunction. Glial observations included an increase in microglial densities and an elevation in glial markers, particularly GFAP [8]. Additionally, ASD tissue has decreased anti-apoptotic proteins and increased pro-apoptotic proteins, which suggest that apoptotic pathways are disrupted in ASD.

The discovered GABAergic and glutamatergic deficits are in line with notions that main neurons have an E/I imbalance in both their output to important limbic cortical targets and their input. This imbalance has an impact on how the brain regulates behaviour and information processing, and it is likely connected to the main symptoms of ASD. Additionally, E/I imbalance may help to explain why seizure disorders and ASD frequently coexist. The abnormal excitatory and inhibitory circuits caused by various genetic perturbations that contribute to both ASD and epilepsy alter the E/I balance, making it a potentially shared mechanism for both diseases [9]. ASD participants' lower GABA and higher glutamate levels were found in various magnetic resonance spectroscopic imaging (MRSI) studies, which is generally consistent with the GABAergic and glutamatergic deficits described in this study.

A number of additional neuroimaging studies, data from animal model studies, electrophysiology, and models based on induced pluripotent stem cell (iPSC) research all confirm the post-mortem findings that E/I imbalance exists. Aberrant apoptotic signalling may be a factor in certain individuals with ASD's increased neuronal counts and more reliable reports of bigger brain sizes.The 4 studies showing decreased anti-apoptotic proteins and/or increased pro-apoptotic proteins in ASD examined brain tissue from donors older than 4 years, which provides strong evidence that there is an initial overgrowth followed by a normalisation of brain size in autism. Head circumference and structural neuroimaging studies of the brain also support this theory. As a result, the tendency towards greater apoptosis in ASD may coincide with the time when growth abruptly stops, resulting in the majority of autistic cases falling within the normal range by adolescence and maturity. In particular cases, abnormal neurogenesis may result from one or more factors, such as the total number of founder cells, the length or number of subsequent cell cycles, the modes of cell division and selective cell death, or neuronal migration [10].

Minicolumnopathy, possibly altered neuronal numbers, and white and grey matter fibres may all be present. About half of those who fulfil the diagnostic criteria for ASD have a learning deficit that may be caused by such generalised processes from a young age. GABAergic synapses depend on PV to maintain their synaptic plasticity, and studies demonstrating its altered expression raise the possibility of diminished synaptic plasticity. The capacity of synapses to become stronger or weaker over time in response to changes in their activity is known as synaptic plasticity. All signs lead to defective synaptic transmission in ASD, including altered levels of proteins involved in the regulation of synaptic vesicles, aberrant gene expression levels of synaptic genes involved in glutamatergic neurotransmission, and synaptic pathways. Results from studies using animal models and iPSCs also lend credence to the synaptic dysfunction theory. In a recent diffusion weighted MRI study, it was discovered that ASD patients between the ages of 8 and 25 have abnormal white matter tract development.

This age range is characterised by increased synaptic proliferation, pruning, and myelination of white matter tracts. Numerous immune system and inflammatory response genes, as well as markers for astrocytes and microglia, are implicated by transcriptomic analysis. Increased expression of the proinflammatory miRNA miR-155p5, which has been linked to a number of inflammatory disorders, has also been repeatedly observed in ASD samples [11]. Similar to this, the increased microglial density throughout the cortex of people with ASD raises the possibility that synaptic or neuronal abnormalities may trigger microglial activation as a neuroimmune system response, which may contribute to the pathophysiology of ASD. Investigating potential neuroinflammation processes in ASD will be made easier by using animal and cellular models.

Our research found no indication of sex-dependent expression, pointing to a more likely explanation for the sex bias in autism that involves continual interaction with sexually dimorphic pathways. Although the evidence is yet weak, reductions in ER- and aromatase activity as well as a drop in RORA protein levels, which is controlled by sex hormones, may help to explain part of this. Additionally, given the general absence of sufficiently large samples to be separated into subgroups and the fact that several sex interactions have not been replicated, some of these "sex effects" in the literature may be spurious false positives owing to multiple hypothesis testing. Several human neuroimaging studies, in contrast to the post-mortem results, point out variations between the sexes' brains [12].

Conclusion

However, post-mortem investigations have enabled many researchers to directly examine ASD brain tissue, enabling the characterisation of autism and similar neurodevelopmental disorders at the level of neuronal populations and the particular neural circuits that they form. Despite the drawbacks of a limited body of research, a number of consistent results of ASD-related changes at the global, regional, cellular, synaptic, and molecular levels have been made, with significant evidence for GABAergic, glutamatergic, and glial dysfunction. Post-mortem research is still an essential tool in the arsenal of neuroscientists, but sample collection and processing may be done more efficiently with international cooperation. Given the early beginning of ASD, investigations should stratify and include a wider range of age groups in their experimental designs to identify potential differences in ASD that may be age-specific. According to the area studied and the purpose of the study, it is crucial to match individuals for age, sex, and PMI as well as take other characteristics, including IQ and co-morbidities, into account. To avoid drawing any incorrect inferences from molecular investigations, it is important to consider a number of pre-mortem and post-mortem aspects of the donated tissues. To close the remaining information gaps, additional in-vitro research utilising animal, cellular, and organoid models as well as deep phenotyping of clinical samples disorders would be needed.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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