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Discordant Symptoms in Monozygotic Twins with Huntington's Disease, Spinocerebellar Ataxia and other Neurodegenerative and Mendelian Disorders

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Abstract

This is a review of nature (genetics) vs. nurture (environment in several genetically based conditions of the brain and nervous system. In the medical literature on twins similar symptoms and progression of the diseases are described as concordant. Symptoms that differ among identical twins are described as discordant. If a genetic condition like Huntington's disease is 100 percent influenced by genetics, then one would expect all Huntington's symptoms to be concordant. If some symptoms are discordant then they are attributed to the environment. Ways to describe these environmental factors include: non-genetic factors, epigenetics, nurture, stochastic (patterns that can't be predicted), pre and post-natal environment, lifestyle, and nutrition. These environmental factors are slightly different or hugely different even for identical twins. The environmental factors, especially lifestyle and nutrition are the factors most influenced by brain health coaches and complementary and alternative medicine practitioners. The literature supports the idea that even in Mendelian disorders (conditions that are thought of as primarily influenced by genetics) the environment, lifestyle, and nutrition can make large differences in the symptom picture and quality of life.

Keywords: Mendelian disorders; Nature; Nurture; Environment; Genetics; Monozygotic twins; Huntington's disease; Episodic ataxia type 1; Spinocerebellar ataxia (SCA1); Machado-Joseph Disease (MJD); Dentatorubro-pallidoluysian atrophy (DRPLA); Familial forms of Alzheimer's disease; Familiar amyloidotic polyneuropathy; Neurofibromatosis type 1; Facioscapulohumeral muscular dystrophy; Myotonic dystrophy; Gerstmann-Straussler-Scheinker disease; Rett syndrome; Joubert syndrome

Introduction

Things that can be different or similar in twins include age at onset, landmarks of the disease process, behavioral abnormalities, severity of chorea or symptoms, mental deficits, clinical expression, motor or muscle related symptoms, attentional impairment, hyperkinetic hypotonic, and more.

Some of the conditions in which discordant symptoms are found in identical twins include: Huntington's disease, Episodic Ataxia Type 1, Spinocerebellar ataxia (SCA1), Machado-Joseph Disease (MJD), Dentatorubro-pallidoluysian Atrophy (DRPLA), Familial forms of Alzheimer's disease, Familiar Amyloidotic Polyneuropathy, Neurofibromatosis type 1, Facioscapulohumeral Muscular Dystrophy, Myotonic Dystrophy, Gerstmann-Straussler-Scheinker disease, Rett Syndrome, and Joubert syndrome.

Literature Review

Here is what the literature says:

Early neurodegeneration (Huntington's, Spinocerebellar ataxias, Alzheimer's)

Monozygotic twins start out exactly the same but the womb environment can influence them differently. One twin can be bigger, taking more nutrients and space. At birth identical twins can be both genetically and non-genetically different. Environmental impacts can start long before birth as researchers point out in this 2012 study. "As monozygotic (MZ) twins are believed to be genetically identical, discordance for disease phenotype between MZ twins has been used in genetic research to understand the contribution of genetic vs environmental factors in disease development. Recent studies show that MZ twins can differ both genetically and epigenetically. MZ twins that are phenotypically discordant for monogenic diseases are of special interest. Such occurrences have been described for Huntington's disease, spinocerebellar ataxias, as well as for familial forms of Alzheimer's disease [1].

Bigger is not always better

Being the bigger twin is not always an advantage as one twins study points out, "Our study results, which included matched preterm twin pairs for study/control groups to evaluate risk factors for the overall evidence of brain injury, could not determine specific risk factors for these brain pathologies. The finding that severe brain pathologies were more common among the larger co-twin requires further study of and attention to short- and long-term outcomes and the potential conflicts that may arise [2].

Huntington's disease

There are still questions about the impact of the environment in Huntington's disease symptoms, even though it has been studied for over 50 years. This early study found little impact and the two following studies were significantly different. In this 1983 study of identical twins raised in different households, researchers noted, "Age at onset, landmarks of the disease, and behavioral abnormalities were strikingly similar [3].

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In a 2007 Huntington's study researchers noted differences in anxiety levels, paranoia, chorea, and motor (muscle) symptoms. Similarities in motor symptoms and signs (more correlated with genetics) and significant differences in mental state symptoms (environment). "Monozygotic male twins, carrying the same number of trinucleotide repeats in the IT 15 Huntington disease (HD) gene, showed a different clinical course. Patient 1 presented with anxiety and chorea at the age of 40. Patient 2 showed persecution paranoia and motor impersistence at the age of 42. On the cognitive and behavior scales, patient 1 showed a significant worsening when compared with patient 2. Our cases support the belief that the motor symptoms and signs in HD are highly dependent on the trinucleotide expansion [4].

Another study of male monozygotic twins concordant for Huntington's disease reported almost the opposite noting similarities in their metal deficit and differences in the severity of their chorea. This indicates that the environment can affect both neurological and mental state symptoms.

Researchers explained, "The monozygosity of the twins and the diagnosis of Huntington's disease are well established. The twins are now age 30, and although the severity of their chorea differs, they have a similar degree of mental deficit. This family is of additional interest because the daughter of one of the twins has childhood Huntington's disease, and the mother of the twins had the adult-onset rigid variant of the disease. Such unusual families afford some insight into the variability of the clinical manifestations of this hereditary disease [5].

Spinocerebellar ataxia (SCA1), Machado-Joseph Disease (MJD), Dentatorubro-pallidoluysian Atrophy (DRPLA)

In these three conditions researchers noted, "The expansion of unstable trinucleotide CAG repeat polymorphisms of a number of genes causes several neurodegenerative disorders with decreased cognitive function, the severity of the disorder being related to allele length at the triplet repeat locus."

Yet they concluded that genetics did not account for cognitive differences. "While association was supported between SCA1 and Cambridge reading scores and between DRPLA and inspection time, results were inconsistent across software packages. Given the number of statistical tests performed, it is unlikely that trinucleotide repeat variation in the normal range for these genes influences variation in normal cognition [6].

This suggests that it is the environment that accounts for cognition differences. The following study also indicates an importance of the environment. "Although phenotypic heterogeneity in autosomal dominant spinocerebellar ataxia (SCA) has been explained in part by genotypic heterogeneity, clinical observations suggest the influence of additional factors." Researchers did quantitative assessments of ocular motor function and postural control in 2 sets of identical twins, one with SCA type 2 and the other with episodic ataxia type 2. They concluded, "We found significant differences in saccade velocity, saccade metrics, and postural stability between each monozygotic twin. The differences point to differential involvement between twins of discrete regions in the cerebellum and brainstem. These results demonstrate the presence of quantitative differences in the severity, rate of progression, and regional central nervous system involvement in monozygotic twins with SCA that must be owing to the existence of nongermline or external factors [7].

Episodic ataxia type 1

Even though episodic ataxia type 1 (EA1) is a monogenic channelopathy caused by mutations of the potassium channel gene KCNA1 there can be significant quality of life differences. Researchers noted in an identical twin study, "Affected individuals carrying the same mutation can exhibit considerable variability in the severity of ataxia, neuromyotonia, and other associated features. We identified a new KCNA1 mutation in each pair of twins. Both pairs reported striking differences in the clinical severity of symptoms. The F414S mutation identified in one set of twins also occurred in a distantly related family in which seizures complicated the EA1 phenotype. These results broaden the range of KCNA1 mutations and reveal an unexpectedly large contribution of non-genetic factors to phenotypic variability in EA1 [8].

Neurofibromaztosis type 1

While the analysis of monozygotic twins (MZ) concordant for neurofibromatosis type 1 (*NF1*) has indicated that genetic factors exert a major influence on the clinical variability (e.g. the number of cafe-au-lait spots and/or neurofibromas), researchers noted differences as well and suggest that mutations (due to environmental factors) may take place a few days after fertilization in the blastosyst stage. "Here, we report on a pair of monozygotic, dichorionic twins who are phenotypically discordant with respect to *NF1*. We conclude that the twinning event, which would have taken place within three days post-fertilization, must have preceded the c.4108C>T mutation which is therefore predicted to have occurred during the blastocyst stage, leading to somatic mosaicism with normal cells lacking the mutation. This is the first reported case of monozygotic twins discordant for *NF1* in whom mosaicism for a postzygotic *NF1* gene mutation has been observed in the affected but not the unaffected twin [9].

Familiar amyloidotic polyneuropathy

These twins were discordant for age of onset which indicates that environmental factors can delay onset of neurodegenerative disorders and increase quality of life. Researchers noted, "Familial amyloidotic polyneuropathy type I (FAP-I), TTR Met 30, was present in two sets of proven monozygotic (MZ) twins. Both pairs [of twins] were discordant for age at onset and some clinical manifestations of FAP-I. We reviewed the differences in age at onset and clinical features in both sets and in two other pairs of presumed MZ twins with FAP-I and compared them with those in MZ twin pairs with other Mendelian disorders, such as neurofibromatosis type 1, Huntington's disease, facioscapulohumeral muscular dystrophy, and myotonic dystrophy. We conclude that, in addition to the postulated modifying genes, there must be a significant contribution from non-genetic factors to the phenotypic variability of FAP-I (age at onset and clinical expression), either because of environmental differences or stochastic events during (or after) the twinning process [10].

Gerstmann-Straussler-Scheinker disease and cerebellar ataxia

Researchers noted significant age of onset differences even though prion protein (PrP) plaque patterns were similar. "Gerstmann-Straussler-Scheinker disease (GSS) is an autosomal, dominantly inherited prion disease. In this study, we present different complicated brain pathologies determined postmortem of monozygotic GSS twin sisters. Case 1 showed cerebellar ataxia at the age of 58 years, and died at 66 years. Case 2 became symptomatic at the age of 75 years, and died at 79 years. There was a 17-year difference in the age of onset between the twins. Postmortem examination revealed numerous prion protein (PrP) plaques in the brains of both cases. PrPres signal patterns were similar between the twins [11].

Rett syndrome

In this study researchers challenge the idea that monozygotic twins can be used to differentiate between what is genetics and what is environmental because even in monozygotic twins they find genetic differences. The thing is that monozygotic twins initially start out identical, until the environment intervenes. That intervention may come a few days after fertilization or years later but the genes are not changing themselves if they are different as they were found to be in this case.

Discussion

Researchers noted, "Monozygotic (identical) twins have been widely used in genetic studies to determine the relative contributions of heredity and the environment in human diseases. Discordance in disease manifestation between affected monozygotic twins has been attributed to either environmental factors or different patterns of X chromosome inactivation (XCI)."

But what is it besides the environment contributes to X chromosome inactivation?

Researchers continue, "Here, we report the genomic and epigenomic sequences in skin fibroblasts of a discordant monozygotic twin pair with Rett syndrome, an X-linked neurodevelopmental disorder characterized by autistic features, epileptic seizures, gait ataxia and stereotypical hand movements. The twins shared the same *de novo* mutation in exon 4 of the *MECP2* gene (G269AfsX288), which was paternal in origin and occurred during spermatogenesis. The XCI patterns in the twins did not differ in lymphocytes, skin fibroblasts, and hair cells (which originate from ectoderm as does neuronal tissue). Differences in DNA methylation between the twins were detected in fibroblasts in the upstream regions of genes involved in brain function and skeletal tissues such as Mohawk Homeobox (MKX), Brain-type Creatine Kinase (CKB), and FYN Tyrosine Kinase Protooncogene (FYN) [12].

Joubert Syndrome

In this case researchers describe "three sisters with Joubert syndrome, two of whom are monozygotic twins with highly discordant phenotypes. The twins were born at 34 weeks' gestation with discordant birth weights. Their anatomic, neurologic, and developmental status differs greatly: Twin B is able to walk, run, and is verbal, unlike Twin A who is wheelchair-bound, severely retarded, nonverbal, and autistic. Abnormal eye movements and retinal dysplasia are striking features in all three girls, but none has renal cysts seen by ultrasonography. Magnetic resonance images show the "molar tooth sign," the radiologic hallmark of Joubert syndrome, although only one twin, the most severely handicapped, has severe hypoplasia of the cerebellar hemispheres. Phenotypic differences between the twins could be attributable to postzygotic unequal division of the inner cell mass, unequal sharing of the venous return from a monochorionic placenta, mosaicism, or a mutation of a modifying gene [13].

Researchers do not speculate on what might cause the unequal division of cell mass, venous return or gene mutations in these twins but even monozygotic twins experience their pre-natal environment differently.

Exercise

In a study to assess whether brain functional and/or structural modulation associated with long-term physical activity is detectable using a discordant monozygotic male twin pair design, researchers noted both functional and structural differences in the brains of the inactive twin as compared with the active twin and said, "We registered somatosensory mismatch response (SMMR) in EEG to electrical stimulation of fingers and whole brain MR images. We obtained exercise history and measured physical fitness and body composition. SMMR dipolar source strengths differed between active and inactive twins within twin pairs in postcentral gyrus, medial frontal gyrus and superior temporal gyrus and in anterior cingulate (AC) GM voxel counts differed similarly. Compared to active twins, their inactive twin brothers showed greater dipole strengths in short periods of the deviant-elicited SMMR and larger AC GM voxel counts. Stronger activation in early unattended cortical processing of the deviant sensory signals in inactive co-twins may imply less effective gating of somatosensory information in inactive twins compared to their active brothers [14].

This somatosensory gating is relevant to focal dystonia and a lack of somatosensory gating can be a sign of brain injury. There are many examples in the medical literature of monozygote twins who have significantly different quality of life, signs and symptoms even when they both have the same neurodegenerative disease, which they inherited.

Conclusion

There are many examples in the medical literature of monozygotic twins who have significantly different quality of life, signs and symptoms even when they both have the same neurodegenerative disease, which they inherited. This research supports the idea that the quality of the environment, lifestyle choices, nutrition and health and wellness can make a significant difference in age of onset of symptoms as well as quality of life after diagnosis.

Conflict of Interest

No financial interest of conflict of interest exists.

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