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Cognition in hereditary ataxia

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Abstract
Apart from motor control the cerebellum has been implicated in higher cortical functions such as memory, fronto-executive functions, visuoconstructive skills and emotion. Clinical descriptions of hereditary ataxias mention cognitive impairment to a variable extent. Systematic neuropsychological studies are limited. Regarding the neuropathological pattern in different SCA types, cognitive deficits in hereditary ataxias are not likely to be contingent upon cerebellar degeneration but to result from disruption of cerebrocerebellar circuitries at various levels in the CNS.

Key words: *Ataxia, cognitive deficits, dominant genes, recessive genes*

Introduction

The hereditary ataxias are a group of genetically defined neurological disorders. The autosomal dominantly inherited spinocerebellar ataxias (SCA) are characterized by degeneration of the cerebellum and its afferent and efferent connections while the most frequent recessive ataxia, Friedreich's ataxia (FA) primarily involves dorsal root ganglia and the spinal cord. During the past few years, there has been increasing awareness of the nonmotor role of the cerebellum: While some investigators failed to provide clear evidence for cognitive deficits in patients with a purely cerebellar syndrome, other clinical and functional imaging studies implicated the cerebellum in higher cognitive functions (1). After the identification of various mutations there is increasing evidence for a considerable overlap of clinical phenotypes in hereditary ataxia. In clinical descriptions of SCA and FA patients, the prevalence and severity of cognitive dysfunction varies considerably. Apart from varying methodological approaches this is likely to result from the variability of extracerebellar involvement not only between but also within the same genotypes. In the following, we will focus on the cognitive profile of the most frequent genetically defined types of hereditary ataxia.

Friedreich's ataxia (FA)

Some earlier studies in patients with a FA phenotype described slowed information processing, impaired verbal learning, visuospatial and executive dysfunction (2–4) that may be accompanied by affective disorders including psychopathic signs and reduced defensiveness (5,6). Other investigators failed to provide clear evidence for cognitive deterioration in FA (7). However, these studies had been undertaken prior to the identification of the FA mutations (3,5) or the clinical diagnosis was not confirmed by molecular genetic analysis (2,6). Patients with other types of ataxia may have been included in these studies. So, these observations may not be attributed to FA without reservation. In a systematic neuropsychological approach, Mantovan described executive and memory problems in 13 patients with a genetic diagnosis of FA (8). Personality changes included increased irritability, impulsiveness, blunting of affect and reduced defensiveness. Neuropsychological testing revealed executive dysfunction with poor concept formation, concrete thinking, slowed information processing and impaired verbal fluency and defective visuospatial memory. Implicit learning was severely impaired as compared to controls. This wide-spread mental deterioration may be partly explained by methodological details: Patients and controls were not matched for education and average IQ; two FA subjects even fell below the normal IQ range. While the test performance was not correlated to GAA repeat size, patients with longer disease durations performed significantly worse than patients with shorter durations (8).

Ataxia with oculomotor apraxia (AOA)

This group of autosomal recessive ataxias includes at least two different genetic entities: ataxia with

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oculomotor apraxia type 1 (AOA1, also called early-onset ataxia with ocular motor apraxia and hypoalbuminaemia) and ataxia with ocular apraxia type 2 with elevated alpha-fetoprotein levels (AOA2). AOA1 is characterized by early-onset cerebellar ataxia, oculomotor apraxia, neuropathy, and mental retardation with additional hypoalbuminaemia and hypercholesterolaemia (9). In a detailed neuropsychological study of six AOA1 patients with normal IQ values there was evidence for memory impairment characterized by disturbed learning and retrieval information. These memory disturbances were associated with executive dysfunction exhibited by difficulties in initiation, conceptualization, reduced verbal fluency and low frontal scores (10). On the contrary, executive dysfunction in AOA2 is so subtle that it can only be revealed by thorough neuropsychological testing (11–13).

Ataxia telangiectasia (AT, Louis-Bar syndrome)

Ataxia telangiectasia (A-T) is a rare, autosomal recessive disorder associated with immunodeficiency, endocrine and skin abnormalities, and a predisposition for lymphoreticular malignancies (14). In a systematic approach, 17 AT individuals were compared to 21 age matched controls. Verbal IQ was found to be significantly lower in the AT group. After statistically controlling for verbal IQ measures, AT exhibited problems in judging explicit time intervals (15).

Spinocerebellar ataxias (SCA)

SCA1

While mild mental deterioration, such as restlessness and emotional instability, have been documented in 5–25% of SCA1 patients of various ethnic origin, severe dementia is restricted to single cases (16–22). Genis described 'frontal-like' symptoms as euphoria and emotional instability in Spanish SCA1 individuals (23). The first systematic neuropsychological approach was undertaken by Kish (24), who reported on general intellectual impairment with defective verbal and non-verbal intelligence, memory and executive function in 11 affected family members from the Schut pedigree, a large North American SCA1 kindred. In this study, the control group was equated for age and educational status but not for IQ and had significantly higher IQ estimates than the SCA1 individuals. This methodological detail may at least partly account for the widespread cognitive deficits observed by Kish. In another neuropsychological study of seven unrelated SCA1 pedigrees, general intellectual impairment was restricted to single patients. Defective verbal memory became evident on a range of memory tests involving both structured and unrelated verbal material. In addition, SCA1 was characterized by perseverations and impaired set shifting (25).

SCA2

In clinical descriptions, the frequency of cognitive deficits varies from 5–19% in SCA2 samples (26–29). Dementia may even dominate the clinical syndrome (28). Psychiatric symptoms including impulsiveness and emotional instability have also been mentioned by several clinical investigators (30). Infantile onset is commonly accompanied by developmental delay and severe cognitive deficits (31). General intellectual deterioration with reduced scores may become evident on the Mini-Mental State Examination (MMSE) in up to 25% of SCA2 patients (32). Non-demented SCA2 subjects exhibit deficits on various tests mainly involving fronto-executive skills (30,32,33). These problems may develop very early in the course of the disease (34) and are neither related to the repeat size nor to the age of onset (30,32). Interestingly, functional imaging studies revealed frontal hypoperfusion in SCA2 individuals with executive dysfunction that were not due to cerebral atrophy (33). Apart from executive dysfunctions, there was evidence for defective verbal memory in SCA2 (32,35). Visuospatial function and memory are not significantly altered in non-demented SCA2 individuals, while demented SCA2 subjects had significant problems in the reproduction of a complex figure (32).

SCA3

Most clinical investigations of SCA3 individuals of various ethnic background emphasize the absence of cognitive dysfunction (36–39). In a large clinical description of Portuguese SCA3 patients, Sequeiros & Coutinho mention mild loss of memory in two out of 143 individuals (40). SCA3 subjects also tend to develop depression and anxiety (41,42). The first neuropsychological study of six Australian SCA3 patients yielded slowed processing of visual information in complex tasks and impaired shifting of visual attention. These findings were ascribed to fronto-executive dysfunction (43). On a test battery mostly mostly relying on verbal skills, SCA3 individuals exhibited problems in phonemic fluency, timed attentional tasks and cognitive flexibility that are consistent with impaired executive function. Defective verbal memory was documented in Japanese, German and Brazilian kindreds (42,44,45). In the Japanese sample, there was also evidence for visual memory, visuospatial and constructional deficits as well as reduced verbal fluency. However, the broad cognitive decline may be overestimated since verbal fluency tasks were correlated to the ataxia scores (42).

SCA6

Most clinical descriptions emphasize the absence of cognitive deficits in SCA6 (46–48). There is one single-case report describing a SCA6 patient with additional mental symptoms of schizophrenia and dementia (49). This patient had a family history of mental disorders without clinical manifestations of ataxia. Neuropsychological data are limited to a single study comparing SCA6 to age- and IQ-matched controls (50). There was no evidence for a statistically significant impairment of attention, verbal memory, visuospatial or fronto-executive functions. On the other hand, SCA6 individuals showed slight, statistically not significant hints for defective verbal memory, verbal fluency and executive function. In addition, two patients with the longest disease durations achieved low scores on the MMSE but did not fulfill the formal criteria for dementia. Clinically, all SCA6 subjects had a purely cerebellar syndrome as demonstrated by clinical and radiological studies (50).

SCA19

Neuropsychological assessment of a Dutch SCA19 pedigree yielded fronto-executive problems associated with global cognitive impairment in some of the more severely affected patients (51).

Comparative studies

Comparing the test profile of five SCA1, eight SCA2, and seven SCA3 individuals and eight age- and IQ-matched controls, executive dysfunction was most prominent in SCA1 as compared to controls and all other SCA types. Mild impairment became evident present on verbal memory tasks in SCA1, SCA2 and SCA3 (45).

Clinical descriptions of other SCAs

In a meta-analysis of unselected clinical series of SCA17 patients, the prevalence of dementia is dependent on the ethnic background. Systematic neuropsychological studies have not been published to date in SCA17. Most clinical investigators emphasize the presence of cognitive deterioration in 50–100% of SCA17 individuals (52). Cognitive abnormalities include impaired concentration, constructional and orofacial apraxia, executive dysfunction with lack of insight, memory impairment, disorientation in space and time. In addition, various psychiatric symptoms (insomnia, restlessness, grimacing, tics, personality changes, mood changes like depression and euphoria, aggressive behavior, self mutilation, hypersexuality, visual hallucinations, psychosis including paranoia, mutism) are part of the 'core syndrome' of SCA17 (52,53). Clinical descriptions of SCA14, a gene encoding a protein kinase, include a very slowly progressive cerebellar ataxia with tremor and myoclonus that may occasionally be associated with executive dysfunction (54,55). SCA10 patients may also develop intellectual decline and psychiatric symptoms (56). It is quite surprising that neuropsychological studies have not been performed to date in dentatorubral-pallidoluysian atrophy (DRPLA). Dementia represents one of its core features apart from ataxia, chorea, myoclonus and epilepsy (57).

Discussion

During the past years, there has been increasing awareness of the nonmotor role of the cerebellum: clinical reports of patients with lesions confined to the cerebellum implicated the cerebellum in higher cognitive functions (58–62). This hypothesis has been supported by functional neuroimaging studies demonstrating cerebellar activation in tests of working memory (63), verbal memory (64), linguistic processing (65,66), motor learning (67), executive function (68), classical conditioning (69), and attention (70). On the contrary, other investigators failed to provide clear evidence for cognitive deficits in patients with cerebellar syndromes (1).

Cerebellar degeneration represents the common feature of all types of hereditary ataxia. Nevertheless, there are considerable differences in the cognitive pattern. If the cerebellum would be the primary source of intellectual dysfunction, one would expect a more homogeneous cognitive decline. Certainly, degenerative changes of cerebellar structures vary between distinct types of hereditary ataxia: While SCA1, 2 and 6 primarily involve the cerebellar cortex, SCA3 is characterized by cerebellar nuclei pathology (71,72). SCA17 shows degeneration of both the cerebellar cortex and the dentate nucleus (73,74). In SCA6, degeneration is almost completely restricted to the cerebellum (49) but this does not produce marked cognitive problems (50). On the other hand, pathological changes in FA first occur in the spinal cord and cerebellar degeneration is usually mild. Nevertheless, intellectual problems are prominent in FA. That is why the cognitive features of hereditary ataxia do not point to an essential cerebellar contribution to higher cognitive functions.

Many of the reports on neuropsychological problems in cerebellar disease included patients with additional extracerebellar damage. Indeed, most other SCA types are characterized by extracerebellar degeneration to a various extent. In SCA1, and SCA2, the degenerative process involves pontine nuclei and inferior olives (23), with additional neuronal loss in the substantia nigra, and the cerebral hemispheres in SCA2 (75–77). In addition to pontine and olivary degeneration, SCA3 is characterized by more severe neuronal loss and gliosis of substantia nigra, internal pallidum and subthalamic nucleus (78).

Deficient memory involving verbal and visual functions has been described in FA and most SCA subtypes. In Alzheimer's disease, degeneration occurs in the basal forebrain cholinergic system which provides the major cholinergic innervation to the neocortex, hippocampus and amygdala. The 'cholinergic hypothesis' of dementia has been supported by post mortem and functional imaging studies demonstrating reduced acetylcholinesterase activity in the cerebral cortex of patients with Alzheimer's disease (79–81). By analogy, having observed general cognitive dysfunction in SCA1 patients, Kish and colleagues analysed cholinergic marker enzymes in the cortices of SCA1 brains and found them considerably reduced (24,2). Cholinergic marker enzymes have not yet been studied in other SCA genotypes. Regarding the close correspondence of SCA1 and SCA2 in every respect, the 'cholinergic hypothesis' could also be taken into consideration to explain the memory deficits and the general intellectual impairment present at least in SCA2.

Another explanation is based on functional imaging studies showing activation of cerebellar and prefrontal areas during the free recall of word lists (64,83). They are in accordance to clinical reports on defective verbal memory in patients with damage to the frontal lobes (84). Defective recall of verbal material may therefore also be interpreted as fronto-executive dysfunction. Executive dysfunction that is also seen in patients with damage to the prefrontal cortex is the most consistent and prominent feature in all types of SCA and FA. Indeed, post-mortem studies show degeneration of the frontal lobes in SCA2 and 17 (27,74,85) but not in SCA3 and SCA1 (23,40,78,86). In FA, cortical atrophy is a late phenomenon, but FA patients with executive deficits show hypoperfusion not only in the cerebellum, but also in frontal cortex and other subcortical areas (8).

Indeed, executive deficits could also originate in subcortical structures. The degenerative process also involves basal ganglia at least in SCA2, and SCA3 (27,75,78,85). Such an assumption is made to explain 'subcortical dementia' in basal ganglia disorders. This concept is based on the disruption of a cortico-striato-thalamic loop at the level of the striatum or the thalamus leading to frontal lobe dysfunction although the frontal lobe is morphologically intact (87). Striatal degeneration is a typical feature in SCA3 (78), but not in SCA 1 or SCA2 (23,27,75,88). Thalamic degeneration has been reported in SCA2 and SCA3 (89,90) but not in SCA1 (23,88). Another explanation for the cognitive deficits in cerebellar disease is the disruption of cerebrocerebellar connections. This circuitry consists of a feedforward limb and a feedback limb (91–93). Efferent connections arising from the dentate nucleus and projecting to the prefrontal cortex thus represent the feedback limb of the cerebrocerebellar circuitry (94–96). The hypothesis of a disrupted cerebrocerebellar circuitry is further supported by functional imaging studies demonstrating cerebellar activation during performance of executive tasks, thus reflecting the close functional relationship between the cerebellum and frontal cortex (68). Feedforward and feedback links between the cerebellum and the parietal cortex also form the theoretical base for a cerebellar involvement in visuospatial organisation (93,97,98). In hereditary ataxia, significant visuospatial deficits are exceptional and accompanied by general intellectual impairment.

All these explanations cannot be applied to the situation in FA. Degeneration in FA starts in the spinal cord to be followed by moderate cerebellar changes. Cerebral atrophy if restricted to late stages of FA (99). Therefore, it is difficult to ascribe neuropsychological and psychiatric impairment to degeneration of cerebellar, cerebral or basal ganglia structures. Reduced Frataxin levels result in deficient mitochondrial energy metabolism. Some groups have speculated that CNS tissues with high energy demand may be more vulnerable than others to frataxin deficiency (8). If Frataxin was important to the energy metabolism of certain CNS structures, its expression would be expected to be physiologically high. Indeed, Frataxin levels are low in the cerebellum and lowest in the cerebral cortex under physiological conditions (100,101). Therefore, this explanation is not very likely to account for the cognitive deficits in FA.

Taken together, the meta-analysis of neuropsychological deficits in hereditary ataxia does not allow clear-cut conclusion on the origin of cognitive dysfunction. Social isolation and limited access to education may also contribute to the impaired test performance in these patients. Neurodegeneration is widespread and variable even within the same genotype. The respective genes are expressed throughout the nervous system. Thus, neuropsychological testing of patients with hereditary ataxia cannot be regarded an appropriate tool to define the cerebellar contribution to higher cortical functions. Instead of circumscribed damage to single anatomical structures, interruption of cerebrocerebellar circuits at various levels suggest itself an appropriate concept of cognitive dysfunction in hereditary ataxia.

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