COGNITIVE AFFECTIVE DISORDER ASSOCIATED WITH RHOMBENCEPHALOSYNAPSYS

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ABSTRACT

Rhombencephalosynapsys (RS) is a rare cerebellar malformation in which the cerebellum is severely underdeveloped. The condition is associated in Gomez Lopez Hernandez syndrome with congenital trigeminal anaesthesia and a self injurious behavior. The cognitive-affective disorder associated with rhomboencephalosynapsis seems to be linked to brain dysfunction: this report supports the theory of a cerebellar contribution to non motor functions (Shachmann, 1998).

1. THE CEREBELLAR COGNITIVE AFFECTIVE SYNDROME (CCAS)

The cerebellum is involved in many cognitive functions, such as level of attention, sensory discrimination, working memory, semantic association, verbal learning and memory, and complex problem solving (Allen, 1997). Attentional and motor task involve different regions of the cerebellum: "cerebellum is not designed to perform a single neurobehavioral function, such as motor control or attention, but instead is a system composed of different
regions that distinctly influence different neurobehavioral functions” (Allen, 1997). Vermis agenesis is experimentally involved in affective control of behavior and in the coordination of fear related somatic and autonomic conditioned responses (Ghelarducci, 1997).

Definition

The cerebellar cognitive affective syndrome is a pattern of behavioural abnormalities (Schmahmann & Sherman, 1998) that includes:

- impairments of executive function (deficient planning, set-shifting, abstract reasoning, working memory, decreased verbal fluency) often with perseveration;
- distractibility or inattention;
- visuo-spatial disorganization and impaired visuo-spatial memory;
- personality change with blunting of affect or disinhibited and inappropriate behavior;
- difficulties with language production including dysprosodia, agrammatism and mild anomia.

The net effect of these disturbances in cognitive abilities appears to be a general lowering of intellectual function.

This syndrome has been first described by Schmahmann & Sherman (1998) in a population of 20 patients with lesions confined to the cerebellum.

The Role of Cerebro-Cerebellar Connections

The constellation of deficits in the cerebellar cognitive affective syndrome is suggestive of disruption of the cerebellar modulation of neural circuits that link prefrontal, posterior, parietal, superior temporal and limbic cortices with the cerebellum. In particular, posterior lobe lesions are mostly important in the generation of the syndrome, and the vermis is consistently involved in patients with pronounced affective presentation, while more pronounced disturbances are present in patients with bilateral and acute disease (Schmahmann & Sherman, 1998).

It has been hypothesized (Schmahmann & Sherman, 1998) that the multiple highly organized anatomical subsystems that constitute the cerebrocerebellar circuit represent functional subsystems that facilitate cerebellar processing in many different functional domains, be they motor, sensory, cognitive, affective or autonomic. The proposed net effect of these multiple streams of diverse information, reaching into and being sent back from the cerebellum is that the cerebellum is able to integrate multiple internal representations with external stimuli and self-generated responses. The cerebellar modulation of these different subsystems permits the ultimate production of harmonious motor, cognitive and affective/autonomic behaviours. The loss of the cerebellar component of these neural circuits produces a dysmetria of thought (Schmahmann, 1991, 1996) that results in the cerebellar cognitive affective syndrome.

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Clinical Presentation

The cerebellar cognitive affective syndrome shows the clinical relevance of the non-motor functions of the cerebellum and supports the evidence for a correlation between cerebellar damage and changes in behavior.

The original arguments supporting the view that the cerebellum might play a significant role in cognitive functions - traditionally the domain of areas such as the prefrontal cortex – come from anatomy, physiology and functional neuroimaging studies.

These arguments are:

1. the observation, during evolution, of the roughly parallel expansion of cerebellar hemispheres with the great enlargement of the neocortex in the primates (Ramnani, 2001);
2. the consideration of the cerebrocerebellar circuits that link the cerebellum with associative and paralimbic cerebral areas that are producing evolving theoretical notions addressing the fundamental role of the cerebellum in motor, sensory, cognitive and affective and autonomic behaviours (Dolan, 1998);
3. the growing collection of a wealth of physiological and behavioural data in experimental animals which confirm the hypothesis of a close interrelation of motor development and cognitive development and of the cerebellum and prefrontal cortex (Diamond, 2000);
4. the hypotization of a similar role of the neocerebellum (vermal and hemispheric portions) in animals, for the regulation of fear related behaviours (Ghelarducci, 1997), and in humans, for the control of affective reactions such as anxiety and fear (Sacchetti, 2002);
5. the findings from functional imaging studies that have shown how the lateral cerebellum becomes active during cognitive tasks that are far removed from control of movement (Ramnani, 2001).

The missing evidence suggesting a role for the cerebellum in higher order functions (Dolan, 1998) was a convincing demonstration of clinically relevant behavioural changes in patients with lesions restricted to the cerebellum; this clinical evidence has been obtained by studies of patients with degenerative diseases of the cerebellum and by the accurate description of their impaired cognitive function and behavioural change (Schmahmann & Sherman, 1998).

These behavioural changes that have been diagnosed at bedside and quantified by neuropsychological tests conform to an identifiable clinical syndrome that is consistent with predictions derived from anatomy, physiology and functional neuroimaging studies.

In affected patients, arousal and alertness are not depressed. Remote episodic and semantic memory are preserved and new learning is only mildly affected. Cerebellar cognitive affective syndrome patients have difficulty with planning and integration of cognitive responses; these deficits are clinically relevant, noted by family members and nursing and medical staff. Other cortical phenomena such as aphasia, apraxia and agnosia are largely absent. Furthermore, the cerebellar cognitive affective syndrome is distinguishable from other subcortical syndromes by virtue of the symptom complex consisting of disturbances in executive, spatial, linguistic and affective functions. The core features of
executive, spatial, linguistic and affective changes set the cerebellar cognitive affective syndrome apart from non specific confusional states or dementia states and other subcortical syndromes.

How to Study CCAS

A complete screening for detecting the main features of the cerebellar cognitive affective syndrome should comprise (Schmahmann 1998):

1. Neurological examinations
2. Bedside mental state tests
3. Neuropsychological testing

Neurological Examinations

The starting point for a diagnosis of cerebellar cognitive affective syndrome is the presence of a cerebellar-related documented deficit in function.

Neurological observation is important because it can detect different movement disorders according to the localization of the cerebellar damage.

On this purpose, neuroimaging investigations can best focus the cerebellar damage while functional brain imaging is very informative in revealing the portion of cerebellum that is activated by a large number of cognitive tasks (devoid of movement) and can help in distinguish the contribution of the lesioned cerebellum to the new abnormal behaviour observed in affected patients.

Bedside Mental State Tests

The CCAS includes alterations in behaviour that extend beyond cognition. Affected patients may experience altered regulation of mood and personality, display obsessive-compulsive tendencies, and demonstrate psychotic thinking (Schmahmann, 2003). A recent review of studies assessing the potential cognitive deficit and personality changes associated with cerebellar disease has pointed out the role of the cerebellum in schizophrenia, dementia, and other psychiatric disorders (Rapoport et al., 2000). The first reports in the 1800’s of the behavioural consequences of cerebellar lesions focused on psychiatric manifestations; cases of intellectual impairment and aberrant behavior in patients with cerebellar disease were described as early as 1831 (Schmahmann, 1997). Later clinical studies identified a relationship between the cerebellum and personality, aggression and emotion, and linked psychosis and schizophrenia in particular with enlargement of the fourth ventricle, smaller cerebellar vermis and cerebellar atrophy. Current studies show changes in cerebellar symmetry and volume in schizophrenics and functional imaging studies reveal differences in metabolic activity in the cerebellum of schizophrenics during tests of language and memory. Vermal and hemispheric atrophy are evident on some MRI studies of autistic subjects, although other investigators conclude that the cerebellar volume is larger than in controls (Schmahmann, 2003). Recent findings suggest that researchers should consider the role of the cerebellum to understand the neurological substrates of behavior (Rapoport et al., 2000) because personality changes of either flattening of affect or disinhibited and inappropriate behavior in patients with CCAS are common. Moreover depression has been shown to be a
recurring problem and it has been hypothesized that cerebellar vermal atrophy may be a late degenerative event in those who have multiple affective episodes (Schmahmann, 2003). Useful instruments adopted in order to evaluate mental state parameters of psychopathology in patients affected by cerebellar cognitive affective syndrome are vermal atrophy may be a late degenerative event in those who have multiple affective episodes (Schmahmann & Sherman, 1998):

- DSM III-R (SCID II; semi-structured interview for the diagnosis of personality disorders; Spitzer et al., 2000).
- ABC (Aberrant Behaviour Checklist; Aman et al., 1985).

Neuropsychological Testing

The major functional category suggested to be addressed in the neuropsychological testing for cerebellar cognitive affective syndrome are:

1. Intellectual functioning
2. Executive functioning
3. Reasoning and abstraction
4. Visuo-spatial/visual construction
5. Language
6. Attention and orientation
7. Verbal and visual memory

In literature, several instruments are reported to be indicated for the specific evaluation of these domains. See the tests listed below:

- Wechsler Adult Intelligence Scale – Revised (WAIS – R; Wechsler, 1981)
- Wechsler Memory Scale – Revised (WMS – R; Wechsler, 1987)
- Rey/Taylor Complex Figure Test (Rey, 1941; Kolb and Whishaw, 1985)
- Controlled Oral Word Association Test (FAS; Yeudell et al., 1986; Spreen and Straus, 1991)
- Animal Naming Test (Spreen and Straus, 1991)
- Stroop Color and Word Test (Golden, 1978)
- Trail Making Test (Army individual Test Battery, 1994)
- Wisconsin Card Sorting Test (Heaton et al., 1993)
- Porteus Maze Test (Porteus, 1965)
- Hooper Visual Organization Test (Hooper, 1983)
- Boston Naming Test (Kaplan et al., 1983)
- Peabody Picture Vocabulary Test – Revised (Dunn & Dunn, 1981)
- California Verbal Learning Test (CVLT; Delis et al., 1987)
- Rey Auditory Verbal Learning Test (RAVLT; Rey, 1958)
- Written Fluency Test (H-words, Reitan, 1979)
Verbal Fluency Test (Novelli et al., 1986)
- Raven’s Standard Progressive Matrices (Raven et al., 1976)
- Benton Judgment of Line Orientation Test (Benton et al., 1983)
- Benton Face Recognition Test (Benton et al., 1983)
- Tower of Hanoi Test (Shallice, 1982; Shallice and Burgess, 1991)
- Wide Range Achievement Test (Wilkinson, 1993)

2. Rombencephalosynapsys

Rhombencephalosynapsys (RS) has been considered a rare malformation with an estimate frequency of 0.13%, but MRI has diagnosed it in many children and adults (Jellinger, 2002).

RS was first described by Obersteiner, on the post mortem examination of a 28 year old suicide victim (Obersteiner, 1916) and called RS by Gross and Hoff in 1959. RS essential features are the absence of the incisura cerebelli posterior, fusion of cerebellar hemispheres, agenesis of the vermis, absence of the velum medullare anterius and nuclei fastigii, and fusion of the dentate nuclei, which are shifted towards the midline (Schachenmeyr, 1982). The first observation and four subsequent cases were all reported in Vienna and for this reason RS was called a “Viennese malformation” (ibidem).

Severe behavioural disorders have been described in most cases (Jellinger, 2002).

Pathogenesis

Rhombencephalosynapsis (RHS) is a rare congenital condition in which the cerebellum is severely underdeveloped. In this anomaly, vermic hypogenesis or agenesis is present and it is not associated with disconnected cerebellar hemispheres, as in Dandy-Walker malformation, “molar-tooth” malformation (an anomaly presented in case of Joubert syndrome), or tecto-cerebellar dysraphia. On the contrary, the cerebellar hemispheres are fused, and the dentate nuclei are closely apposed.

The pathogenesis of this unique malformation of the posterior fossa remains unclear, also because occasional cytogenetic studies in patients with RHS resulted negative. Sarnat (2001) suggested that RHS is probably a genetic disease, representing an underexpression of a dorsalizing organizer gene.

Embryologically, RHS is likely to represent an early developmental derangement, probably occurring at Carnegie stages 14-17 (28-41 days of gestation).

Rhombencephalon (hindbrain), the most caudal part of the encephalon, formed at stage 11, promptly divides in metencephalon (future pons and cerebellum) and myelencephalon (future medulla oblongata). The embryonic cerebellum (tuberculum cerebelli) first appears as a proliferation of cells in the alar laminae of the metencephalon: it consists of a band of tissue in the dorsal part of the first rhombomere and straddles the midline in the shape of an inverted “V”. During the thirds gestational month, the midline component shows accelerated growth and begins to fill the acute angle between the limbs of the inverted V. The two cerebellar primordes unite dorsally to form a median, worm-like mass, the vermis.
The lateral parts, i.e. the cerebellar hemispheres, grow rapidly. The cerebellar fissures begin to form at about the 12th week of gestation in the transverse axis of the cerebellum. The primary fissure divides the medial part of the cerebellum into the anterior vermis and the posterior vermis, so that vermian differentiation occurs first in the most posterior (caudal) part and proceeds toward the anterior (rostral) part. Finally, the cerebellum becomes connected to the midbrain, pons and medulla by bundles of fibres called the superior, middle and inferior cerebellar peduncles respectively.

In RHS, absence of the vermis finally results in abnormal cerebellar hemispheric fusion, malorientation of folia and a unique horseshoe-shaped dentate nucleus, that appears to be draped posteriorly to the fourth ventricle. While cerebellar findings are quite similar in all patients affected by RHS, associated supratentorial abnormalities can be very different. Hydrocephalus, secondary to aqueductal stenosis, absence or hypoplasia of the corpus callosum, the anterior commissura, and the septum pellucidum, nodular heterotopia, fused fornices, fused thalami, and hypoplasia of the temporal lobes were also described. These supratentorial anomalies, which often dominate the clinical features, are consistent with the suggested gestational timing of RHS. They all, in fact, may represent malformation in ventral induction, which occur at the same time the cerebellum is developing.

It is worthwhile to be noticed that development of the posterior fossa differs significantly from that of the supratentorial brain. Whereas the telencephalon undergoes a normal cleavage process known as diverticulation, following a midline to lateral pathway, the cerebellum arises from two distinct embryonic primordia, and the median vermis forms in a second time from the lateral hemispheres following a lateral to midline direction. So, the vermis represents the only cerebellar interhemispheric connection, whereas the peduncles allow cerebellar communication with the brainstem and the remainder of the central system.

**Neuropathology**

The first report of rhombencephalosynapsis was described by Obersteiner in 1916. Schachenmayr described the absence of the olfactory tracts, bulbs and septum pellucidum in concert with the posterior fossa malformation (Schachenmayr, 1982). Rhombencephalosynapsis appears to represent a unique malformation of the posterior fossa, however variable supratentorial anomalies have occasionally been reported such as abnormal gyri, diminished white matter, fused cerebral peduncles, thalami and fornices, hydrocephalus, agenesis of the septum pellucidum, hypoplasia or aplasia of anterior commissure, agenesis of olfactory tracts, dysgenetic corpus callosum, meningoencephalocele, schizencephaly, anomalies related to hypothalamic–hypophyseal axis, and thalamic fusion (Taori, 2003). Moreover, in the reports by Gross and Kepes, rhombencephalosynapsis was associated with thalamic fusion and third ventricular deficiency. It is interesting to know that the hypothalamic–pituitary axis appeared normal in all cases but one (Taori, 2003). In that case, the posterior pituitary lobe was absent, the septum pellucidum was absent, and the optic nerves, chiasm, and tracts were markedly hypoplastic, fulfilling the pathologic diagnosis of septo-optic dysplasia [Michaud, 1982; Truwit, 1991]. Nevertheless, in only two cases the corpus callosum was described as hypoplastic or dysgenetic (Taori 2003). Rhombencephalosynapsis thus appears to represent a unique malformation of the posterior fossa with occasional supratentorial, midline anomalies,
most likely related to the gestational age at the time of insult to the developing rhombencephalon. The severity of clinical manifestations and the prognosis of rhombencephalosynapsis generally depend on the associated supratentorial anomalies. Cakirer (2003) summarizes both the similarities and differences between Joubert syndrome and rhombencephalosynapsis in terms of their clinical and radiological aspects. The main common feature of these two anomalies is aplasia or hypoplasia of the cerebellar vermis associated with a malformed cerebellum and fourth ventricle. Distinguishing features include: (a) apposition of cerebellar hemispheres that may be associated with a vermian cleft in Joubert syndrome vs the fusion of cerebellar hemispheres across the midline in rhombencephalosynapsis; (b) the thickened and elongated superior cerebellar peduncles causing molar tooth sign in Joubert syndrome versus the fusion of peduncles in rhombencephalosynapsis; (c) the absence of vermian folial pattern in Joubert syndrome versus abnormal orientation of folia in rhombencephalosynapsis; (d) the dysplasia and heterotopia of dentate nuclei in Joubert syndrome versus fusion of nuclei across the midline; (e) the presence of isthmic dysgenesis and brain stem tract and nucleus anomalies in Joubert syndrome; (f) the fusion of inferior colliculi in rhombencephalosynapsis; (g) the more common association of supratentorial anomalies and hydrocephalus in rhombencephalosynapsis; and (h) the more common association of extracranial anomalies in Joubert syndrome make the differentiation of these two developmental anomalies easy with neuroimaging studies, especially MRI.

Genetics

All published cases have been sporadic. A single instance of consanguinity was signaled by Romanengo (1997), who suggests the possibility of autosomal recessive inheritance. Karyotype was normal in all reported cases except in a case reported by Truwit (1991) where an interstitial deletion of the long arm of chromosome 2 has been detected.

The pathogenesis of RS is obscure, however recently an animal model, Dreher Lmx 1a gene mutant mouse, has been proposed (Jellinger, 2002). This model shows agenesis of the vermis with fusion of cerebellar hemispheres and inferior colliculi due to dorsal patterning defects in the hindbrain, resembling human RS. The autosomal recessive mutation of the recently identified LIM homeobox gene includes misplaced neurons in numerous patterns of the CNS which mimic a spectrum of neuronal migration disorders in human, probably due to disruption of the glial limiting membrane (Costa, 2000). LIM – home box genes play an essential role in patterning and differentiation of different cell types during embryonic development (Zhao, 2000). Experimental studies on the genetic control of early regional specification of brain stem structures have identified a critical organizer center for cerebellar development: the isthmic organizer (Hatten, 1995) which is localized at the hind-midbrain transition and controls anterior hindbrain and midbrain regionalization (Martínez, 2000). It is possible that mutations of genes that regulate early specification of cerebellar domain, particularly the homeotic genes that establish the dorsal isthmic region, might produce the alterations found in RS (Yachnis, 2002).
Associated Anomalies

The clinical presentation associated with RS is extremely variable ranging from mild truncal ataxia to severe cerebral palsy and mental retardation (Toelle, 2002). The degree of mental retardation is also very variable, from mild to severe. Reported cases were from different age groups, the youngest being reported antenatally (Litherland, 1993) and the oldest being a 39 years old living patient (Montull, 2000; Taori, 2003).

The last author reviewed from literature 23 cases with sufficient clinical data and signalled 6 new cases. All published cases have been sporadic. Ataxia was reported in 12/23 patients. Head rolling was reported in 4 patients. Epilepsy was reported in 7 patients. Seizures were also present in one of the autopsy cases reported by Gross (1959).

Hand anomalies have been reported by Aydingoz (1997) in a RS subject, namely phalangeal hypoplasia and occult polydactyly in the right hand and syndactyly in the left. Outside the central nervous system, the musculoskeletal system is the commonest site of associated anomalies in case with RS: Michaud (1982) described a case of RS in a severely malformed newborn who died in the first day of life with hypoplasia of the right hand and multiple segmentation defect of the cervical and thoracic vertebrae and left upper ribs. Facial anomalies have been described by Romanengo (1997): low set ears, long philtrum, hypertelorism and strabismus.

Cardiovascular, respiratory, and urinary system anomalies are very rarely associated extracranial findings (Taori, 2003).

MR Imaging

The MR features of RS are characteristic. The posterior fossa is small; no cyst is present. In a sagittal section, the fourth ventricle appears narrowed. The fastigium is formed, and the nodulus seems to be the only component of the vermis, and determinates a protuberance below the fastigium. On axial sections, the fourth ventricle does not appear with the normal crescentic shape, but it is deformed, with a typical diamond-shaped morphology described as tear-drop, or keyhole. This abnormal configuration of the fourth ventricle results from the dorsal and rostral convergence of the dentate nuclei, the cerebellar peduncles, and the inferior colliculi. It is also due to the absence of the vermis, that normally shapes the floor of the fourth ventricle. Further distinctive features are a flat and uninterrupted continuity of the base of the cerebellar hemispheres, clearly evident in coronal sections, transversely orientated folia and fissures in the inferior cerebellum, that extend directly across the midline, and large corpus medullare, all of which represent the single-lobed cerebellum.

Behavioral Disorders, RS and Gomez Lopez Hernandez Syndrome

Behavioral disturbances have been reported in RS. The first report of rhombencephalosynapsis, was about the post mortem examination of a 28 year old suicide victim (Obersteiner, 1916). No clinical data were known about the patient. However, we know his profession (Kanzleigehilfe), so we suppose he had no mental retardation. Compulsive head rolling was signaled by Demarel (1994) in a 6-year old boy affected by RS
and a behavioral disorder-associated with psychomotor epilepsy has been described in another RS patient, diagnosed with MRI (Savolaine, 1991). Autoaggressive behaviour has been described by Toelle in his second patient (2002).

Self injurious behavior has been reported in all patients with Gomez Lopez Hernandez (GLH) syndrome, characterized by RS, congenital trigeminal anaesthesia and alopecia. GLH syndrome, also called cerebello-trigeminal dermal dysplasia, has been described for the first time by Gomez in 1979. A few patients with GLH have been described since 1979 (Gomez 1979; Lopez-Hernandez 1982; Pascual Castroviejo 1983; Gomez 1987; Munoz 1997; Brocks 2000). It is interesting to note that Gross in the autopsy of his two RS patients in 1959, signalled in both cases two symmetric circumscribed areas of hair loss (symmetrische umschriebene Defekte der Kopfthaarung). Normal chromosomal analysis has been reported in all the patients. The syndrome seems to be sporadic or autosomal recessive (OMIM). Physical examination is characterized by towerlike skull, flat forehead and occiput-bilateral parietal areas of alopecia. Craniosynostosis has been described in all patients. Other dysmorphic features are midfacial hypoplasia, bilateral corneal opacities, ocular hypertelorism-telecanthus, low set ears. Clinodactyly of fifth fingers is reported frequently. Growth is impaired: all patients range less than the third percentile in height and weight. From the neurological point of view, cerebellar ataxia and corneal and facial anaesthesia of trigeminal distribution have been described in all subjects. A MRI imaging of rhombencephalosynapsis associated with hypoplasia of trigeminal nuclei is present in all subjects. Cognitive aspects are characterized by mild to severe mental retardation. Hyperactivity, depression, self injurious behavior, bipolar disorders have been reported in these subjects. Self injurious behavior may be partially due to the lack of sensory sensation to the face and eyes (Brocks, 2000). Life expectancy is not known, but all the described cases are very young (the oldest is 19 yrs old).

Case Report

Since 1996 we are following a young patient (S.A.) affected by RS who came to observation for oral self mutilation (Verri, 2000): now he is becoming increasingly alcohol addicted (with a week-end modality).

The patient was born on the 30th week of pregnancy: neonatal weight was 2 kg. Delayed psychomotor development was evident since early neonatal period; he was able to walk alone only at the age of 2; he had however problems with balance till the age of 3.

Learning problems were evident at the primary school. During late infancy, compulsive head rolling was signaled. The patient is actually working as labourer.

From the age of 19 yrs, he started to compulsively touch his teeth and his gums. For this reason he developed oral infections followed by lost of all his teeth. He got recurrent implantology.

At the age of 22 he was hospitalized because of a suspected neoplasm of the mouth (Fig 1). An oral mucosal biopsy documented a granuloma with a secondary infection. Subsequently, he was hospitalized in our Neurological Institute, to clarify his clinical symptomatology.

The objective evaluation documented dysmorphic features (little dysmorphic ears, cubitum valgum, hypertelorism, pes cavum) and bitemporal balding (Fig.2 and Fig. 3).
Neurological evaluation showed a slight truncal ataxia and right trigeminal hypoestesia. Bilateral keratoconus has been signalled by the ophthalmologist.

Fig.1: Presenting oral lesion of the patient S.A.

Fig 2: The 28yrs old patient (frontal view): see hypertelorism and bitemporal balding.
Chromosomal analysis was normal. Routine biochemical analyses were normal.

**Neurophysiological Evaluation**

To evaluate trigeminal function, the patient was submitted to an electromyographic (EMG) study of masseter muscle by coaxial-needle electrode, exteroceptive suppression reflexes of masseter muscle by infraorbital foramen stimulation, and blink reflex. Neurogenic findings represented by an increased area of motor unit action potentials (MUAPs) and poor recruitments of the interference pattern were observed in the right masseter muscle; normal EMG findings were obtained in left muscle.

Exteroceptive suppression (ES) reflexes of the masseter muscle revealed absence of both first and second inhibitory components (ES1 and ES2) of the right masseter muscle when stimulating the omolateral infraorbital foramen; normal latencies and duration of ES1 and ES2 components were obtained in the contralateral muscle when stimulating the left infraorbital foramen.

The stimulation of the left side showed normal latencies and duration for both ES1 and ES2.

Blink reflex by stimulating the right side revealed absence of R1 direct component with latencies of R2 components (direct and contralateral) prolonged, whereas the stimulus of the left side showed R1 and R2 (direct and contralateral) with normal latency (Fig.4). These
findings indicate a severe sensory deficit strictly unilateral of the first trigeminal branch. An alteration of peripheral motor axons of the trigeminal nerve in the side involved was indicated by the EMG findings of the masseter muscle and by the absence strictly unilateral of ES1 and ES2 reflexes.

Fig 4: Blink reflex by supraorbital nerve stimulation in patient with Gomez Lopez Hernandez syndrome. D: direct response; C: controlateral response. Absence of R1 response (R1?) and delayed latency of R2 D response by stimulating the right side.

Therefore electrophysiological study showed abnormalities in both sensory and motor pathways of the trigeminal nerve.

Neuroradiological Findings

NMR, performed by a Philips "Gyroscan T5" 0,5 Jesk tool documented a typical picture of rhombencephalosynapsis, characterized by fusion of cerebellar hemispheres, abnormal transversal orientation of cerebellar folia, and vermian agenesis, with narrowing and posterior pointing of the fourth ventricle (Fig.5,6,7). No associated supratentorial anomalies were demonstrated.
Fig 5: Sagittal T1-IR weighted image shows the abnormal aspect of the cerebellum: on the midline the medial part of cerebellar hemispheres, instead of the vermis, are evident. The fourth ventricle is narrow.

Fig. 6: Axial T2-weighted image shows the so-called “teardrop” shape of the fourth ventricle.
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Fig. 7: Coronal T1-IR weighted image shows the fusion of the cerebellar hemispheres on the midline, the transverse orientation of the cerebellar folia and the flat aspect of the basis of the olocerebellum.

Cognitive-Behavioural Assessment

The evaluation with DSM-IV criteria documented an obsessive-compulsive personality disorder on axis II associated with emotional instability; Cognitive Behavioral Assessment (C.B.A.) (Sanavio 1986) documented a mild obsessive-compulsive disorder; Aberrant Behavior Checklist (ABC) (Aman 1985) documented a stereotipic, self injurious behavior.

The patient was sufficiently autonomous and able to work: Adaptive Behaviour Inventory (Brown-Leigh 1987) points out a good level of autonomy.

During the various sessions of assessment S.A. was generally collaborating: he gladly participated to the talks and executed the proposed tasks with adequate levels of attention and concentration. He was sociable and wasn’t frightened of the situation; the language was rather simple, at times stereotyped and there were some expressive difficulties due to the consequences of the oral self mutilations. However he answered pertinently to the questions: he was well oriented in space and time and gladly spoke about his own interests and activities. Sometimes he appeared uninhibited and his attitude was rather childish: he laughed, he joked, he spoke loudly and addressed the examiner like a friend, often using expressions from his dialect. In any case he showed good understanding: he quickly understood the instructions and he was able to remember them throughout the tasks. Sometimes he looked like restless, especially when he performed the more complex tasks and he frequently showed
the tendency to give impulsive answers; anyway his attention ability and his motivation levels seemed to be adequate.

The following instruments were administered: Wechsler Adult Intelligence Scale (WAIS), Token Test; Coloured Progressive Matrices (CPM); Ray Taylor Complex Figure Test; Rey Auditory Verbal Learning Test (RAVLT); Verbal Fluency; Stroop Test; Trail Making Test; Wisconsin Card Sorting Test (WCST). (Table 1).

To the Wechsler Adult Intelligence Scale (WAIS) S.A. obtained a Full Scale IQ = 74 (mild mental retardation score) with a light discrepancy among the verbal subtests (Verbal IQ = 79, low average score) and the performance subtests (Performance I.Q. = 72, mild mental retardation score).

Verbal subtests showed poor attentive skills and short-term memory (at the “digit span” S.A. was able to repeat five numbers forward and four in reverse sequence) and a limited fund of knowledge acquired through school and cultural experience (“information”). Abstract and understanding, as tested by “similarities” and “comprehension” respectively, where simple, with limited ability to synthesize verbal relationships and restricted practical information and social knowledge. S.A. had limited computational skills: at the “arithmetic” he was able to solve only those tasks requiring the use of one single of the four fundamental arithmetical operations (addition, subtraction, multiplication and division). But, above all, he had poor verbal competences and verbal language (at the “vocabulary” he was able to report the meant of only few simple terms as, for instance, “winter” or “to repair”).

Performance subtests revealed accuracy and speed of visual motor coordination and good scanning ability (“coding”) but impairments in nonverbal reasoning and logical sequencing (“picture arrangement”), in visual-spatial organization (“block design”) and, above all, in the organization of the perception and the reconstruction of concrete shapes (“object assembly”).

Token Test showed good understanding of spoken language, while the performance at Coloured Progressive Matrices (CPM) revealed reduced efficiency in the logical-deductive and abstract reasoning.

Visual-spatial organizational skills as assessed by the Rey Complex Figure Copy seemed to be fairly good: S.A. completed the design rather quickly (approximately 300 second), he copied all the elements of the figure and placed them in the correct position, even if he lost the proportions between the various parts. On the other hand, his visual-spatial memory seemed to be severely impaired: in the Rey Complex Figure Memory S.A. only reproduced the outline of the figure and little elements to its inside; anyway, those that he designed were correctly placed.

In the Rey Auditory Verbal Learning Test (RAVLT) S.A. showed good ability in verbal list learning and memory tasks: he was able to immediately remember approximately 11 words out of 15 listed and recalled 10 out of these at 5 min.

Verbal Fluency tasks revealed severe impairment in the phonemic fluency: S.A. was able to say approximately six word in the specified time (one minute) for each letter of the alphabet presented (“F”, “P”, “L”). The semantic fluency seemed to be in the norm: in a minute S.A. was able to name approximately 16 words belonging to each category (“animals”, “cars”, “fruit”).

Selective and focused attention, mental control and response flexibility as assessed by the Stroop Test seemed to be fairly good. Also the Trail Making Test task A showed average attention and visual-motor tracking skills, while the task B revealed a reduced efficiency in divided attention and ability to shift.
S.A. performance at the Wisconsin Card Sorting Test (WCST) fell within the average: he was able to complete all the 6 categories in 86 matching out of 128, even if he took several trials to establish the first matching criterion, showing reduced cognitive intuition and difficulties in hypothesis generation. His abstract reasoning seemed to be quite perseverative, even if there were not large differences in comparison with the performance of the greater part of the subjects of his age. (T score range 45-54). Moreover, S.A. seemed to be able to establish and maintain adequate problem-solving strategies and to use response feedback information to improve his performance.

**Table 1: Cognitive Assessment Results for instruments with normative data.**

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<td><strong>WAIS</strong></td>
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<td></td>
</tr>
<tr>
<td>Full Scale IQ</td>
<td>74</td>
<td>100 ±15</td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>79</td>
<td>100 ±15</td>
</tr>
<tr>
<td>Performance IQ</td>
<td>72</td>
<td>100 ±15</td>
</tr>
<tr>
<td>Token Test</td>
<td>34</td>
<td>34.45 ±1.58</td>
</tr>
<tr>
<td>CPM</td>
<td>20</td>
<td>36.18 ±7.43</td>
</tr>
<tr>
<td>Trail Making Test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Task A</td>
<td>42 (sec)</td>
<td>28.02 (sec) ±8.78</td>
</tr>
<tr>
<td>Task B</td>
<td>200 (sec)</td>
<td>72.30 (sec) ±28.55</td>
</tr>
<tr>
<td>RAVLT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repetition</td>
<td>57</td>
<td>50.12 ±8.35</td>
</tr>
<tr>
<td>Delayed Recall</td>
<td>10</td>
<td>11.37 ±2.17</td>
</tr>
<tr>
<td>Verbal Fluency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phonological</td>
<td>19</td>
<td>35.09 ±9.84</td>
</tr>
<tr>
<td>Semantic</td>
<td>46</td>
<td>42.74 ±6.96</td>
</tr>
</tbody>
</table>

**3. DISCUSSION**

The cognitive-affective disorder associated with rhomboencephalosynapsis seems to be linked to brain dysfunction: this report supports the theory of a cerebellar contribution to non motor functions (Schachmann, 1998).

In our patient, performance IQ is slightly lower than verbal IQ. A difference between performance IQ and verbal IQ has been reported in congenital ataxia (Steinlin, 1999). Neuropsychological evaluation documented a disturbance of executive functions (particularly nonverbal reasoning and planning), impaired visuospatial memory and reduced phonetic fluency, which have been reported in the cerebellar cognitive affective syndrome (Schmahmann, 2002). The evaluation with DSM-IV criteria documented an obsessive-compulsive personality disorder on axis II and a stereotypic self injurious behavior.

Behavioral alterations are very severe and are mainly characterized by compulsive touching of the mouth with consequent infections.
Self-injurious behavior occurring in persons with mental retardation is a clinically significant and poorly understood problem (King, 1998). It is more frequent in subjects with sensory impairment, autism and severe intellectual disability (Oliver, 1987).

Compulsive self-injurious behavior has been described in disorders with known dysmethylabolic pathogenesis as in Lesh-Nyhan disease (Lesh & Nyhan, 1964) or in other disorders secondary to chromosomal abnormalities (Cornelia de Lange syndrome, Smith Magenis syndrome, Prader Willi and so on) (Deb, 1998). Different types of self injurious behavior have been described in different conditions. Self Injurious Behavior in many respects is becoming a model for the study of gene-brain-behavior relationships in developmental disabilities (Schroder, 2001). For example in Smith Magenis syndrome, the number of different types of self injurious behaviors exhibited was also directly correlated with level of intellectual functioning (Finucane, 2001).

Nyhan proposed a neurotransmitter hypothesis for the autoaggressive compulsive behavior in Lesh Nyhan disease suggesting an impaired dopaminergic and serotoninergic pathways (Nyhan, 1996).

However the autoaggressive behaviour often is evident in disabled subjects and is considered as a psychopathological answer to their condition probably due to a selective vulnerability impairment of a specific neuroaxonal systems.

Functional self mutilation is performed knowingly, as a response to certain stimuli and may or may not serve as a positive purpose (Altom, 1989). On the contrary, we were impressed by the apparent compulsiveness of the injurious behavior of our patient; he frequently asked to his parents to be restricted with hands bandages and he became anxious when the bandages were removed. Self restraint is very common (12-50% from prevalence studies) in individuals with intellectual disabilities who engage in self injurious behaviour (Forman, 2002).

The neurobiology of repetitive movement disorders (stereotyped, self injurious and repetitive behavior) in mentally retarded people is supposed to be related to a developmental insult to central dopamine and serotonin systems (Lewis, 1995). Current findings support a dopamine deficiency model and suggest the efficacy of serotoninergic medications (ibidem). These were relatively ineffective in our patient.

King (1998) considers multiple neurotransmitter systems implicated in the pathogenesis of self injurious behavior, particularly dopaminergic, opioidergic, and serotoninergic systems. Pemoline, a central stimulant, administered systemically at high doses reliably produces self-biting behavior in the rat. The systemic bolus of pemoline produces sustained neostriatal levels of pemoline for over 24 h in a continuous infusion paradigm. Studies of the effect of cortical lesions on pemoline-mediated behaviors reveal that cortical damage, as is common in profound mental retardation, lowers the threshold for pemoline-induced self-biting behavior. Data from the corticostriatal slice suggests that sustained exposure to pemoline produces a shift in N-methyl-D-aspartate receptor-mediated responses rendering them more susceptible to dopaminergic enhancement. Thus, dopaminergic and glutamatergic interactions appear to play an important role in the development and expression of self-biting in the pemoline model (King, 1998).

Though a wide range of self mutilations in mentally retarded as well in psychotic state have been described, oral self mutilation, particularly autoextraction, is rare (Altom, 1989; Armstrong, 1999). The most common topographies reported are head banding, biting, head biting, body hitting and scratching (Hyman, 1990).
Self injurious behaviour has been reported in all patients affected by GLH and was characterized by scarring of the face and head banging (Brocks, 2000). The GLH patient reported by Brocks presented hyperactivity at 4 years, leading to the diagnosis of attention deficit disorder with age progression. Self injurious behaviour initially noted at 2 year progressed when he became older. This along with depression (the patient was diagnosed as having bipolar disorder) and suicidal tendencies necessitated continuous monitoring by age 17. Behavioural problems and suicidal behaviour have been reported also in individuals with apparent isolated rhomboencephalosynapsis. Up to date, anomalies of the cerebellar vermis has been reported in affective disorders (Shah, 1992) and in autism (Hashimoto 1989, Courchesne 1991, 1994, 1998). Recently, a MRI volumetric study tested the differences in vermis volume between autistic subjects, Down and fragile X (Kaufmann 2003). Posterior lobules vermi (lobules VI-VII and VIII-X) were markedly smaller in both Down syndrome groups and those with fragile X syndrome only, whereas only lobules VI-VII were reduced in idiopathic autism. The authors conclude that selective posterior vermis hypoplasia is seen not only in idiopathic autism but also in Down syndrome and some individuals with fragile X syndrome. However, reductions in vermian lobules VI and VII appear to be specific to idiopathic autism, whereas increased size of lobules VI and VII is associated with autism in fragile X syndrome. The latter results are consistent with MRI studies showing lobules VI-VII hyperplasia in a subset of subjects with idiopathic autism and cerebral and hippocampal enlargements in fragile X syndrome (Kaufmann, 2003). Purkinje cell atrophy in autism with significant neurohistological heterogeneity among individuals diagnosed with this disorder has been also described (Fatemi, 2002). Neuroanatomic imaging in autism had suggested a role of cerebellar anomalies among individuals diagnosed with this disorder since many years (Courchesne, 1988) The cerebellum was the only anatomical structure for which there is both imaging and autopsy evidence of abnormality based on data gathered by many laboratories (Courchesne, 1991). Neurophysiologic and neuropsychologic studies of children with hemicerebellar resections and children with autism present an entirely new picture of the role of the cerebellum in normal human cognition in general and in the development of the social and communication deficits in autism in particular (Courchesne, 1991). These studies show that autistic subjects and patients with acquired cerebellar damage are unable to rapidly shift their mental focus of attention. In patients with autism, neocerebellar abnormality may directly impair cognitive functions; may indirectly affect, through its connections to the brain stem, hypothalamus, and thalamus, the development and functioning of one or more systems involved in cognitive, sensory, autonomic, and motor activities; or may occur concomitantly with damage to other neural sites whose dysfunction directly underlies the cognitive deficits in autism (Courchesne, 1988). Attention to understanding normal and abnormal development of the hind brain is a key to define the genesis of autism spectrum disorders (Sulik, 2002).

Neocerebellar congenital maldevelopment has to be considered a significant risk factor not only for neurological but also for cognitive and behavioral disabilities. A global cerebellar impairment may be diagnosed in RS: dysregulation of movement causes ataxia and dysregulation of thoughts and emotion causes cerebellar cognitive affective syndrome (Schmahmann, 2002).

The clinical spectrum of anomalies associated with RS will be better evaluated with the evolution of clinical and genetic research. In particular the connection between sporadic RS and GLH syndrome needs to be clarified. We recommend that a neurophysiological evaluation of trigeminal function be performed in all patients with RS; in fact, the GLH
syndrome may be underdiagnosed. An electrophysiological evaluation identifies in the trigeminal areas objective abnormalities which would otherwise not be recognizable by clinical investigation since an important intellectual disability is common in these patients.

**REFERENCES**


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Cognitive Affective Disorder Associated with Rhombencephalosynapsys


