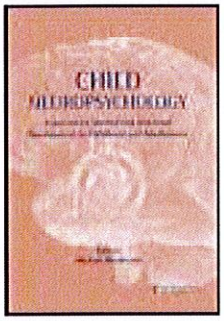

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Psychomotor and cognitive impairments of children with CHARGE syndrome: Common and variable features

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Psychomotor and cognitive impairments of children with CHARGE syndrome: Common and variable features

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Objective: We aimed to understand the mechanisms and sources of learning difficulties in children with CHARGE syndrome who attend school and to determine any specific developmental characteristics.
Method: We analyzed the psychomotor and cognitive functions of eight children from 7 to 13 years old with classical CHARGE syndrome by using the Wechsler Intelligence Scale for Children (WISC), the Neuropsychomotor test (NP-MOT), and several subtests of the Developmental neuropsychological assessment (NEPSY) and Kaufman Assessment Battery for Children (K-ABC) instruments.
Results: The IQ range was from 54 to 92. The main weaknesses related to three domains: static and dynamic postural control, visuospatio-constructive abilities, and both sequential processing and selective attention. The main strengths were in holistic perception, semantic competencies, logical reasoning and planning skills, with axial and peripheral hypotonia. The extent of psychomotor and cognitive deficits was not associated with severity of sensorial deficiencies. We discuss the multiple causal mechanisms of psychomotor and cognitive difficulties.
Conclusion: We found a persistent and homogeneous psychomotor profile and specific cognitive difficulties in 8 children with CHARGE syndrome despite their large range of IQs. Highlighting these specific impairments is important to understand the nature and mechanisms of CHARGE for adapting educational and rehabilitation methods. These problems may be explained by sensory deficits, as well as dysfunction in integrating and/or regulatory regions of the brain.

Keywords: CHARGE syndrome; Neurodevelopment; Muscle tone; Vestibular function; Neuropsychomotor assessment.

The syndrome CHARGE (Coloboma; Heart: cardiac anomalies; choanal Atresia; growth and developmental Retardation; Genital and pubertal anomalies; Ear: ear and auditory anomalies, encompassing multiple congenital anomalies) was described by Hall in 1979

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and named by Pagon, Graham, Zonana, and Yong in 1981 (Blake & Prasad, 2006). The anomalies are not permanent and the phenotype varies greatly among individuals (Russel-Eggitt, Blake, Taylor, & Wyse, 1990; Wright, Brown, Meyerhoff, & Rutledge, 1986). Since the initial description, four other described anomalies have been found frequently and have a good specificity: vestibular anomalies (Abadie et al., 2000; Lemmerling et al., 1998), hyposmia due to a rhinencephalon anomaly explaining the hypogenitalism (Azoulay et al., 2005; Bergman, Bocca, Hoefsloot, Meiners, & van Ravenswaaij-Arts, 2011; Chalouhi et al., 2005; Pinto et al., 2005), dysfunction of the brainstem and cranial nerves, and facial morphologic anomalies (Blake et al., 1998; Blake, Hartshorne, Lawand, Dailor, & Thelin, 2008). Several less-specific anomalies may also be observed: renal, urinary tract, and skeletal anomalies or cleft lip and/or cleft palate. In 2004, CHD7 was identified as the major gene involved in CHARGE syndrome. It encodes a protein of the chromodomain family and is mutated in about two-thirds of CHARGE patients (Lalani et al., 2006; Sanlaville & Verloes, 2006; Vissers et al., 2004; Zentner, Layman, Martin, & Scacheri, 2010).

Most patients with CHARGE syndrome have delayed psychomotor and/or cognitive development. Only a few studies have precisely described the psychomotor and cognitive features because poor cognitive capacity and/or sensorial deficits may impede the administration of tests and interpretation of their results (Harvey, Leaper & Bankier, 1991). The psychomotor and cognitive impairments of children with CHARGE syndrome have multiple origins, both somatic (visual, auditory, vestibular, olfactory, cerebral lesions, etc.) and psychological (long initial hospitalization, lack of care, parental stress, etc.). This multiplicity induces various symptoms and outcomes.

The cognitive capacity of patients with CHARGE ranges widely, from severe disability to high school capability. Nevertheless, from our experience as pediatricians and neuropsychologists, children with CHARGE syndrome have some similarities in functioning that do not depend on their cognitive capacity. The common cognitive and behavioral characteristics may be due in part to their psychomotor and multisensory deficits. Most patients experience delays in steps of verticalization for which they usually compensate fairly well (Abadie et al., 2000; Admiraal & Huygen, 1997; Blake, Russel-Eggitt, Morgan, Ratcliffe, & Wyse, 1990; Thelin & Fussner, 2005). Despite several sensory defects, most of these children learn basic skills. However, at school age, other learning difficulties often appear, especially in mathematics and geometry. These cognitive difficulties are often associated with an inability to adapt to educational systems as well as fatigue, which leads to deviant behaviors and failure in school. Over time, the children often exhibit behavioral problems such as lack of impulse control, restlessness, deviant attitudes, and autistic characteristics (Bernstein & Denno, 2005; Fernell et al., 1999; Graham, Rosner, Dykens, & Visootsak, 2005; Hartshorne, Hefner, & Davenport, 2005; Salem-Hartshorne & Jacob, 2005; Smith, Nichols, Issekutz, & Blake, 2005).

To understand these impairments in children with CHARGE syndrome, we first determined whether such children, who have been walking for a long time, still exhibit psychomotor difficulties. Second, we investigated the cerebral processes that underlie the difficulties and competencies observed to determine whether the difficulties result from multisensory integration defects or lesions of higher cerebral pathways such as frontal areas of the brain. We investigated a small series of children with CHARGE syndrome who had sufficiently high-cognitive levels to attend school. We measured IQ levels, tested neuropsychomotor status and assessed several neuropsychological processes. We tried to understand variations and similarities in results to confirm our hypotheses, to aid in our

interpretation of difficulties in such children, and to provide suggestions for more adapted rehabilitation programs for such children.

PATIENTS AND METHODS

Patients

We included children who were clinically diagnosed with typical CHARGE syndrome in our pediatric unit. CHARGE syndrome is defined as typical when the patient has four major criteria or three major and three minor criteria that have been described in 1998 by an expert team of geneticians (Blake et al., 1998, Blake & Prasad, 2006). The children all had a level of oral language that allowed them to complete the verbal WISC and the NEPSY tests. We included 8 patients at least 7 years old (7 boys; $M_{age} = 9.84$; $SD = 1.53$; $Mdn = 9.86$; range = 7–13) who were enrolled in a regular school (normal class with outside rehabilitation support or special class for deaf or blind children) or a special school for deaf and/or blind children. The socio-professional levels of the parents ranged from employees ($n = 2$) and intermediate professionals ($n = 3$) to management and high-level professionals ($n = 3$). All parents were involved in their children's treatment and were supportive of their learning.

Sensory and Cerebral Characteristics of Patients.

Vision. Children exhibited a wide range of visual deficits: Three had good vision (no coloboma or slight unilateral coloboma: P1, P2, and P7), 3 had highly impaired vision (P3, P4, and P5), and 2 had mildly impaired vision (P6 and P8). Ocular motility was disturbed in half of the children (P2, P3, P5, and P8).

Audition. Hearing loss was mild, moderate, or severe but successfully corrected by mechanical amplification. P7 had the worst hearing loss.

Balance. All patients had total or partial semicircular canal agenesis on a CT scan (total for 6 children; partial for 2: P5 and P7), with partially intact otolithic function for three of four who had undergone functional vestibular assessment (P1, P6, P8). The ages at walking ranged from 20 months (P7) to 30 months (P1).

Half of the children (P1, P4, P6, P7) had major neonatal somatic disorders that were repaired (neonatal surgery, tracheotomy, gastrostomy, cleft lip and palate repairs) but required periods of hospitalization exceeding 6 months.

Brain imaging studies (CT scan or MRI) showed ventricular dilatations, small brainstems, cerebellum anomalies, and disorders of the rhinencephalon, but the analysis of the anomalies was not conclusive because the examinations had been performed early in life. Clinical data are summarized in Table 1.

Methods

All children were examined by an identical protocol by the same examiner under the same conditions. This examiner has had a long experience with children with sensory disabilities and tried to reduce the children's difficulties, especially visual difficulties, by lighting the table, adjusting the child's position, giving more time, and reassuring

Table 1 Clinical Characteristics of the Eight Children with CHARGE Syndrome.

	Auditory	Vision	Oculo-motricity difficulties	Balance	Initial hospitalization lasting > 6 months
P1	Moderate conductive hearing loss: 60 dB	No coloboma	No	No canalar response otolithic OK	Yes
P2	Mild conductive hearing loss: 35 dB R, 60 dB L	Small bilateral papillar coloboma, no macular lesion	Yes	ND	No
P3	Mild conductive hearing loss: 40 dB	Unilateral microphtalmia, controlateral retinal coloboma without macular lesion	Yes	ND	No
P4	Mild conductive hearing loss: 35 dB R, 60 dB L	Unilateral blindness	No	ND	No
P5	Severe hearing loss: 60 dB R, 70 dB L	Unilateral blindness Large contralateral retinal coloboma without macular lesion	Yes	No canalar response, weak otolithic function	No
P6	Moderate hearing loss: 45 dB	Small unilateral papillar coloboma; no macular lesion	No	No canalar response otolithic OK	No
P7	Profound hearing loss	No coloboma	No	ND	
P8	Severe hearing loss: 70 dB	Small unilateral papillar coloboma; no macular lesion	Yes	No canalar response	No

Note. R = right; L = left, dB = decibel; ND = not done.

the children. Children completed an IQ test, the French translation of the WISC-III scale (Wechsler scale), with 10 subtests resulting in three scores: Full-scale IQ, verbal IQ, and performance IQ (Wechsler, 1996). The other subtests were chosen from tests standardized for investigating neuropsychomotor functions, visuoattentional function, visuopracto-spacial function, short-term memory ability, planning, and logical reasoning. Linguistic function and long-term episodic memory ability were not investigated.

Neuropsychomotor Assessment. Neuropsychomotor assessments involved the NP-MOT, a French standardized battery of tests for assessing child neuropsychomotor functions (Vaivre-Douret, 1997, 2002, 2006; Vaivre-Douret et al., 2011). The NP-MOT test-retest reliability ranges from 70% to 98%. Correlation coefficients are .72 to .84 for the NP-MOT battery and the Lincoln Oseretsky Motor Development Scale (LOMDS) (Psychomotor Developmental Scale of Lincoln-Oseretsky), similar to

the Bruininks-Oseretsky Test of Motor Proficiency (BOTMP; Bruininks, 1978) subtests for upper-limb coordination, balance, and bilateral coordination. This battery aims to investigate passive muscle tone (shoulders, limbs, and trunk), standing and synkinesia, static and dynamic balance, tonic laterality (extensibility and dangling of hands and feet to identify the tonic dominant side), laterality of use, fine-digit movements, digital tactile gnosis, and body spatial integration (knowing left from right: for oneself and that of others, and with regard to objects). The test of imitation of distal gestures (Vaivre-Douret, 2002) evaluates the capacity of the child to imitate the configurations of the positions of the fingers and the hands of the examiner facing the child. Data from these tests are expressed as mean and standard deviation (from + 2 *SD* to −2 *SD*).

Tests for Evaluating Visuospatial and Constructive Functions. Children with CHARGE syndrome often have difficulties reproducing models of drawings and/or learning writing (when the shape of the letter is unknown), but they can be good at drawing if the subject is optional. Thus, we administered three subtests involving copying geometrical figures to evaluate visuomotor and spatio-constructive skills. These figures could be simple, requiring holistic mental processing, or complex, without any meaning. The subtests included the "copying" test of the Rey's Figure, which is similar to the English complex figure test of Corwin and Bylsma (Corwin, Bylsma, & Osterrieth, 1993; Rey, 1959), and the "figure copying" test of the NEPSY (Korkman, Kirk, & Kemp, 1997), which measures aptitude for copying a series of figures of increasing complexity. The third test was the "triangle" subtest of the K-ABC test (Kaufman & Kaufman, 1993), which evaluates the mental processes (simultaneous versus sequential) involved in training. Graphomotor skills are not involved in this last subtest.

Tests for Evaluating Short-Term Memory. Because of the learning difficulties of children with CHARGE syndrome, we evaluated short-term memory, that is, the ability to reproduce a series of movements or to repeat numbers or sentences. We used the "hand movements" subtest of the K-ABC, which measures the ability to memorize a random series of hand positions and to reproduce them, the "number repetition" subtest of the WISC, which evaluates the ability to encode and report a series of numbers, and the "phrase repetition" subtest of the NEPSY, which measures the ability to memorize phrases of increasing length and complexity.

Test for Evaluating Functions Related to Logical Reasoning, Planning Skills and Selective Attention. Children with CHARGE often have problems with executive functions (planning, control, and regulation of thinking and actions), too much impulsivity, lack of self-control, attention deficit, and task organization, for example. We used three NEPSY tests: (a) the "tower" test, similar to the London tower test (Shallice, 1982), which evaluates some executive functions in that the child has to move three different-colored bowls following several rules until a goal position is attained (the test evaluates anticipation capacity, planning skills, and the elaboration of new solutions and does not require much motor or spatial constructive ability); (b) the "visual attention" subtest, which includes two subtests requiring the child to detect 20 items randomly scattered among "strangers" (one subtest consists of simple items and the other more complex items); and (c) the "narrative memory" subtest, which measures the aptitude to memorize and put the components of a story in the proper order.

RESULTS

Intelligence Quotients

The WISC results showed a broad range of IQs from 54 to 92 for the full-scale IQ, 48 to 96 for verbal IQ, and 59 to 94 for performance IQ (Table 2). The lowest median score was obtained with the nonverbal subtests. The most consistently poor results occurred with the code subtest (median score = 2/20). No pattern emerged in subtest scores. In this small series, we did not find any association of IQ score and severity of sensory deficits or neonatal history.

Neuropsychomotor Tests

With the NP-MOT, all children presented impaired axial tone: trunk extensibility ($SD = -2$, $n = 3$; $SD = -1$, $n = 5$) and shoulder extensibility ($SD = -2$, $n = 4$; $SD = -1$, $n = 3$). All children had poor scores for subtests evaluating standing muscle tone ($SD = -2$, $n = 6$; $SD = -1$, $n = 2$). Most children presented peripheral hypotonia: wrist dangling ($SD = -2$, $n = 5$; $SD = -1$, $n = 1$) and wrist extensibility ($SD = -2$, $n = 4$; $SD = -1$, $n = 2$). The children did not show tonic laterality with age as do normal children. For all children, postural control was affected in global motor coordination, as shown by results of tests for measuring dynamic balance ($SD = -2$, $n = 7$; $SD = -1$, $n = 1$) and static balance ($SD = -2$, $n = 6$, $SD = -1$, $n = 2$). Indeed, no child could avoid stopping in the jumping exercise, and children were unable to perform the test for static balancing on one foot with eyes open. For most children (6), motor flexibility in fine movements (repetitive or alternating) was affected in "index finger-thumb touching" ($SD = -2$, $n = 3$; $SD = -1$, $n = 3$) and "successive touching thumb to finger tips" ($SD = -2$, $n = 4$; $SD = -1$, $n = 2$). Movements were too rapid and rushed (7 children) or too slow (Patient 7).

Half of the children showed spatial orientation of the body in relation to oneself and to others, but most (6) did not show orientation in terms of an object. Laterality of use was well established, unilateral, and confirmed in 7 children (but not for the youngest). Six children were right-handed, an identical proportion to that in the general population (75%).

Most children (except P5) had normal results for tests that evaluate imitating distal gestures and the test of digital gnosis (again except P5). The children performed well

Table 2 IQ of Eight Children with CHARGE Syndrome Tested by the Wechsler Intelligence Scale for Children.

Patient	Verbal IQ	Performance IQ	Full Scale IQ
P1	62	76	65
P2	96	70	81
P3	76	80	75
P4	85	60	69
P5	85	59	68
P6	58	74	62
P7	91	94	92
P8	48	67	54
Mean	75.1	72.5	70.75
Median	80	73	68.5
SD	16.1	10.65	11

on tests of adaptation and precision of gestures oriented toward a goal when engaging in manipulating real objects (test for picking up coins, manipulating a matchbox, etc.).

Regarding synkinesia, most children (5) were within the normal range qualitatively and quantitatively. P1 and P2 showed facial synkinesia (rapid alternating movement test). Only P6 showed imitative synkinesia. We observed no distal abnormalities of voluntary motricity (as phasic stretch) indicating a disorder of the pyramidal tract (Table 3).

Cognitive Tests

All children showed significant distortions and simplification during the Rey's Figure copying test. Seven children completed the test quickly but with sloppy results. Only P6 took a long time. Disparities in performance by age ranged from −3 years (P7) to −7/8 years (P8). Graphomotor performance was difficult for all children, especially in terms of regulating muscle tone. Seven children showed great haste at the beginning of the copying movement and difficulties in slowing down at the end. The last child (P7) had too much tonic gesture and excessive slowness. The scores were lower for the Rey's Figure reproduction-from-memory test than the copying test. Child P7, who performed the best under copying conditions, required a lot of time for the reproduction-from-memory test because of an inability to recall the figure. The results of the NEPSY figure-copying test were below average for all children. Nevertheless, all children could reproduce simple or meaningful figures (Items 1–8, 10, 15, and 18). All children had difficulties in visuospatial and constructive abilities in the "triangle" subtest of the K-ABC.

Most children (except P2 and P8) had difficulties on the "hand-moving" subtest of the K-ABC ($Mdn = 7.5$ [1–11]). The same six children had severe difficulties on the WISC number-memory subtest (short-term memory). In the NEPSY "phrase-repetition" subtest, all children had difficulty with long phrases. Failure was due to inaccuracies in vocabulary and forgetfulness, but all children but P8 had no confusion with meaning.

In the NEPSY "Tower test," scores for 7 children were above average (P7 scored 9/20). All children could draw because of previously learned procedures for resolving more complex problems. However, most found initiating new procedures that break with established habits difficult because of their impulsivity (they needed to become aware of their mistakes, which they immediately corrected). Regardless, the scores for all children were about or above average.

Results for simple items of the NESPY "visual attention" test were good for all children. Conversely, for complex items (with several criteria), most children (6) had poor results. For the NEPSY "narrative memory" test, only two children (P1 and P6) had severe difficulty in repeating by memory, in the right order, the sequences of the story. One (P8) confused meanings. Conversely, the 5 other children understood the meaning of the story (Table 4).

DISCUSSION

We investigated 8 children with CHARGE syndrome. These children had been able to walk for a long time but still had motor disorders and they had an intellectual level sufficient for school learning but still displayed some cognitive difficulties. Despite a wide range of IQs, they had similar strengths and weaknesses. The main weaknesses involved three domains: static and dynamic postural control, visuospatio-constructive abilities, and

Table 3 Results of Neuropsychomotor Assessments with the NP-MOT for Eight Children with CHARGE Syndrome.

	Muscle Tone and Balance						Body Spatial Orientation			Fine Motricity				
Patient	Dynamic balance	Static balance	Trunk extens.	Shoulder extens.	Wrist dangling	Wrist extens.	Body spatial integration // oneself	Body spatial integration // others	Body spatial integration // object	Thumb/fingers opposition	Fine digital mov.	Digital Tactile gnosis	Gestureimit.	Syncinesia
P1	−2 *SD*	−2	−2	−2	−2	−2	+	−	−	−2	−2	*M*	*M*	−2
P2	−2 *SD*	−1	−1	−1	*M*	*M*	+	+	+	*M*	*M*	+ 1	*M*	−1
P3	−2 *SD*	−2	−1	−2	−2	−1	+	+	+	*M*	−1	*M*	*M*	+ 1
P4	−2 *SD*	−2	−2	*M*	*M*	−1	+	+	−	−2	*M*	*M*	*M*	+ 1
P5	−2 *SD*	−2	−1	−2	−2	−2	−	−	−	−2	−2	−2	−2	*M*
P6	−2 *SD*	−2	−2	−2	−2	−2	−	−	−	−2	−2	*M*	*M*	−2
P7	−2 *SD*	−2	−1	−1	−1	*M*	+	+	−	−1	−1	+ 1	*M*	*M*
P8	−1 *SD*	−1	−1	−1	−2	−2	−	−	−	−1	−1	*M*	*M*	*M*

Note. For muscle tone and balance and fine motricity items, the numbers in the table are standard deviation (*SD*). For body spatial orientation, the items are scored + for passing the test and - for failing the test. Extens.: extension; mov.: movement; imit.: imitation. *M*: mean.

Table 4 Results of Cognitive Tests for Eight Children with CHARGE Syndrome.

	Score for Test Evaluating Visuospatial and Constructive Functions			Score for Test Evaluating Short-Term Memory			Score for Test Evaluating Functions Relating to Logical Reasoning, Planning Skills, and Selective Attention		
Patient	Rey's Figure	Figure Copying NEPSY	Triangle K-ABC	Number Repetition WISC	Hand Movements K-ABC	Phrase Repetition NEPSY	Tower test NEPSY	Visual attention NEPSY	Narrative memory NEPSY
P1	Not done	3	6	3	1		14	9	1
P2	−4.3 y	2	4	12	9		12	13	16
P3	−4.5 y	8	7	1	7		9	11	9
P4	−4.6 y	2	4	8	8		12	4	8
P5	−4.5 y	1	4	3	7		13	6	8
P6	−5.6 y	1	4	1	3		13	5	1
P7	−3 y	6	7	5	7		13	8	10
P8	−8 y	1	4	10	11		12	13	1
Median	−4.5 y	2	4.5	4	7.5		12.5	8.5	8
Range	−3 to -8 y	1 to 8	4 to 7	1 to 12	1 to 11		9 to 14	4 to 13	1 to 16

Note. Results for the Rey's figure test are by age level. For all other subtests, the scores are relative to a total score of 20 points. y = years.

both sequential processing and selective attention. The main strengths concern holistic perception, semantic competences, logical reasoning, and planning skills with axial and peripheral hypotonia.

Problems in Static and Dynamic Postural Control

Two main functions are involved in postural control: orientation and stabilization (Amblard, Crémieux, Marchand, & Carblanc, 1985). Postural orientation is defined by the position of the body segments in relation to each other and in relation to the environment. Postural stabilization corresponds to maintaining balance. The coordination of orientation and stabilization provides stable bases for perception and action (Mallau, Viel, Vaugoyau, & Assaiante, 2006). Our children showed impaired development of both orientation and stabilization functions. Almost all children showed global hypotonia of tone, which leads to impaired tonic laterality, delayed spatial orientation, and poor stabilization skills. For example, they had difficulty standing on one foot with their eyes open or stopping their jump with feet together. All had learned to run and some could even ride a bicycle but after a long and difficult training process.

In normal children, control of posture develops with the influence of sensory information — visual, vestibular, proprioceptive, and tactile. In infants, vision has a major role in the development of both static and dynamic postural control (Bertenthal, Rose, & Bai, 1997; Mallau et al., 2006). Of interest, despite the good vision of our children, several had poor postural control. Their visual deficit was not sufficient to explain the postural control problems. Vestibular function is certainly involved, but since all the children had vestibular lesions, the role of this function was difficult to quantify. We previously suggested that residual otolithic function may have a positive role in postural control (Abadie et al., 2000), but in the current series, too few children had a complete vestibular assessment to confirm these data. Of note, P6 showed major disorders in postural and static motor control despite good visual and otolithic function, which suggests the involvement of other factors. Postural strategies take a long time to mature during human development and depend highly on experience (Hadders-Algra, Brogren, & Forssberg, 1997). For example, postural control of standing becomes proactive (i.e., the child is capable of anticipating perturbations linked to changes in the distribution of force in the body) starting when the child learns to walk (Barela, Jeka, & Clark, 1999). In normal children, anticipative phenomena during walking are comparable to that of adults only at about 8 years of age (Ledebt, 2002). Studies of the development of anticipated postural adjustment have shown how posture integrates anticipation of postural changes with voluntary movements progressively during development (Jover & Mellier, 2005). Of note, during situations of internal anticipation (i.e., walking on a narrow support or jumping in a limited zone with the feet together), anticipated postural adjustments depend on the internal representation that children have of their body. This representation includes the geometry and the kinetics of the body (Massion, 1992). During the first months of life, the elaboration of these kinetic representations is anchored in the child's experience. Little by little, the infant activates automatic feedback mechanisms, which allow for regaining balance after a perturbation (Forssberg & Hirschfeld, 1994; Horak & Nashner, 1986). This feedback is partly kinesthetic and partly visuovestibular. The visuovestibular feedbacks are altered in CHARGE syndrome because of its effect on the semicircular canals. Furthermore, long periods of hospitalization during the first months of life are responsible for defects in active experimentation with negative consequences on the elaboration of kinetic representations of

the body. For example, Patient 8 had the best muscle tone. He had no visual or otolithic defects and never experienced a long period of immobilization. However, P6, who also had preserved visual and otolithic functions, had undergone a tracheotomy and a long hospitalization and had worse psychomotor test results than P8. Relations between medical conditions and behavioral characteristics in patients with CHARGE syndrome are complex and controversial (Vervloed et al., 2006). Previously, length of initial hospitalizations was found correlated with long-term severity of autistic symptoms (Hartschorne et al., 2005), but our previous study found no correlation with scholastic progress (Raqbi et al., 2003).

Our findings may be related to the brain regions implicated in the regulation of muscle tone and posture: the brainstem, vestibular nuclei and tracts, and the cerebellum. The vestibular nuclei are connected directly to the flocculo-nodular lobe, the zone of the cerebellum implicated in the regulation of tone, axial motor function, and, therefore, posture (Guyton, 1991). The peripheral vestibular effect in CHARGE is known; these children may have central vestibular effects. Anomalies of the posterior fossa such as cerebellar atrophy and hypoplasia of the cerebellar vermis and small brainstem are now regularly screened by MRI in children with CHARGE syndrome. The implication of multiple factors and their combination explain the postural deficits in children with CHARGE syndrome. This hypothesis supports the theory of dynamic systems, which considers motor development as emerging from the dynamic and necessary conjunction of three factors: the organism, the environment, and the task (Thelen, 1995; Thelen, Kelso, & Fogel, 1987).

Although global motor function was affected in all our children, fine motor control features were more diverse. Difficulties in fine distal motility regulation (thumb-touch test, opposition of the thumb and the other fingers) were substantial in half of the children and moderate for the others. In handwriting and drawing skills, the difficulty was expressed by impulsivity and by problems in initiating or stopping the movement. In normal children, links form during development between posture and gesture (Ajuriaguerra, 1977; Bullinger, 2003; Fagard, 2000). The quality of the postural adaptation is implicated in the regulation and organization of fine manual movements, especially complex ones (Vaivre-Douret, 2007; Vaivre-Douret et al., 2011).

Impaired Visuospatial and Constructive Functions

All of our children showed difficulties in reproducing complex figures such as the Rey Figure. However, the children could reproduce figures if they were simple (or had a meaning); most children reproduced the Rey's Figure little by little, fragment by fragment, without taking hidden geometric elements into consideration, such as the large rectangle, which they did not treat as a whole figure. However, the rectangle was correctly named and reproduced when it was by itself. The children concentrated on details to the detriment of the whole. There were distortions rather than aberrations in the final result. Only two children took the hidden elements such as the large rectangle into account, but they went too fast, hurried over the task and omitted most of the details. Performing this task efficiently requires rapidly stringing together a series of small movements of the eyes and the head, which allows for exploring the model (presented horizontally) and passing rapidly from the model to the paper where the figure must be reproduced. Therefore, the task is a perceptive and motor task, during which several subtasks must be strung together (exploration of the object, spatial orientation, graphic action). The spatial references implicated in these actions are multiple: retinal-centered (coding according to the position of the image on the retina), oculo-centered (coding according to the position of the eye in the orbit), and

object-centered (coding according to the intrinsic properties of the object), in relation to the head (coding according to the position of the head in relation to the body) or in relation to the axis of the body. For example, in accomplishing a series of eye movements, different references are implicated in the execution of the first eye movement (selecting the object, retino-centered coding) and the second eye movement (oculo-centered coding of the intrinsic properties of the object) (Andersen, Snyder, Li, & Stricanne, 1993; Vergilino-Perez & Beauvillain, 2005). For the duration of the test, the children must rapidly execute a change of references. Little by little, with experience, these rapid passages from one reference to the other become automatic. Moreover, in reproducing a fixed model, the knowledge subjects have of their own kinetics has a direct influence on the perception of the model (Orliaguet & Louis-Dam, 2002). In normal children, this automation is based on visual afferents and visuovestibular afferents that allow for stabilization of the images on the retina during the rapid movements of the head and on somato-sensorial afferents, which control the posture and regulation of fine distal movements (Lopez, Lacour, & Borel, 2005). Clearly, children with CHARGE syndrome have difficulties in these tasks. Unfortunately, during their schooling, they are frequently confronted with learning strategies based on visuospatio-constructive competencies, and their slowness leads to failure in activities such as learning sign language, geometry, and reproducing drawings.

Specific Cognitive Impairments

Six of our children had significant problems in immediately reproducing sequences of items they saw or heard. Of note, the children achieved similar scores in both tests by imitating sequences of items, one in the visuogestual mode (movements of the hands in the K-ABC) and the other in the auditory-verbal mode (memory of the numbers subtest of the WISC). This finding corroborates the idea of a common module that treats brief stimuli with rapid changes in both auditory and visual modes (Habib, 2000; Stein & Walsh, 1997). We found that the severity of these sequential difficulties was not related to the severity of the sensory deficits. These difficulties in sequential processes must be identified in deaf children because visuosequential codes might be suggested and would not be appropriate for them. For two of our children, good results in short-term memory recall suggested that their sequential difficulties could be compensated by their semantic capacity.

The three main domains of altered functions (posturo-motor, visuoconstructive, and sequential processes) in CHARGE syndrome are caused by peripheral sensory deficits and their combinations, but also perhaps lesions of cerebral regulatory regions involved in multisensory integration (brainstem, cerebellum, and associative posterior cortex). For several years, a deficit in multisensory integration explaining part of the problems of children with CHARGE syndrome has been suggested (Brown, 1995). Our clinical observations confirm this hypothesis. The role of problems in multisensory integration in behavioral and cognitive difficulties in CHARGE syndrome can be compared to present studies that link autism to defects in sensory integration (Oberman & Ramachandran, 2008; Russo et al., 2010). This finding may explain the frequency of autistic-like behaviors in children with CHARGE syndrome being due to organic rather than psychological factors, in addition to the obvious role of peripheral sensory defects.

Our children had some preserved reasoning abilities, planning skills, and selective visual attention when sequential memory, visuospatial or motor ability were not involved ("tower" test) and when they did not have to deal with several criteria at the same time

(visual-attention test). They were competent in skills that engage holistic or verbal processes and that involve logic without visuospatial or motor ability. These results may appear to contradict those of Hartshorne and colleagues, who showed problems in executive functions in children with CHARGE syndrome (Hartshorne, Nicholas, Grialou, & Russ, 2007; Nicholas, 2005). These studies were based on questionnaires such as the Behavior Rating Inventory of Executive Function (BRIEF), which evaluate the child's behavior at home and at school in terms of executive functions (inhibiting, shifting, emotional control, initiating, working memory, planning/organizing, organizing materials, and monitoring). However, our results do not contradict those of Hartshorne and colleagues because certain problems observed in children with CHARGE syndrome considered related to execution may result not from dysfunction of the prefrontal cerebral area but rather dysfunction of the ascending tracts that underlie the regulation of action. Reexamining the results of the BRIEF questionnaire would be of interest to determine whether performance is better for questions involving concrete, simple, and significant items than others.

Whatever neurosensory basis, the psychomotor, sensory, and cognitive deficiencies of CHARGE syndrome may create major scholastic problems for older children. The attention span is difficult to maintain and children require strong efforts to maintain postural control when sitting for a long time at school, which makes them easily tired and has a deleterious effect on performance. The children are slow in handwriting tasks, which require fluid gestures that must be executed rapidly. Most encounter difficulties at the end of their primary education, in geometry, geography, and "plastic" arts, all disciplines for which the acquisition of skills occurs through exercises in reproduction. Furthermore, many children with CHARGE syndrome have problems in mathematics because it requires sequential processes. Social interactions also require knowledge of how to manage space. Problems in waiting one's turn to talk, difficulties in anticipation, and the impulsivity of these children may have a motor basis as well as (and not only) a psychological one, which suggests other therapeutic approaches.

Despite our small sample size and inclusion of children with relatively good functioning, these data should allow for understanding children with CHARGE syndrome better and avoiding misunderstandings. Such children should begin psychomotor stimulation early to encourage multisensory integration. At school, short classes are favored, a comfortable and stabilizing chair should be provided, permanent visual aids that do not require sequential processes should be used, and learning should start with the concrete and significant to permit direct access to the senses. Physiotherapy could be proposed for older children, even after the acquisition of walking and early learning tasks.

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