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PHYSICAL AND DEVELOPMENTAL PHENOTYPE ANALYSES IN A BOY WITH WOLF-HIRSCHHORN SYNDROME

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Summary: *Physical and developmental phenotype analyses in a boy with Wolf-Hirschhorn syndrome:* Wolf-Hirschhorn syndrome (WHS) is a rare genetic condition with characteristic facial traits, organ malformations, functional impairment and developmental delay due to partial short arm monosomy of chromosome 4. Although several hundreds of cases have been published to date, a systematic collection of its clinical symptoms and anthropological traits is missing in the literature, and reports on abilities and needs of children with WHS are scanty. Results of detailed physical and developmental phenotype analyses in a 1 10/12-year-old boy with monosomy 4p15.2-pter are presented. Physical analyses were based on systematic data acquisition. They disclosed a total of 32 clinical symptoms and 46 anthropological traits. Developmental analyses were based on the child's interactive play in an environment structured according to Montessori principles. They disclosed a total of 44 abilities and a number of needs to be satisfied by the environment for the support of the child's psychic and intellectual growth. While the physical phenotype is important for the diagnostic process, the developmental phenotype is essential for parental counseling.

Key-words: Wolf-Hirschhorn syndrome – Monosomy 4pter-15.2 – Systematic phenotype analyses – Clinical symptoms – Anthropological traits – Developmental abilities – Educational needs – Montessori principles.

INTRODUCTION

Wolf-Hirschhorn syndrome (WHS, OMIM #194190) is a rare genetic condition with characteristic facial appearance, microsomy, several malformations, neurological changes, motor developmental delay, and severe mental deficiency (6, 7, 23). There are two proposed WHS critical regions, both mapping to the band 4p16.3 (13) and comprising about 165 kb (26) or 300-600 kb (27). Available reports on the physical phenotype indicate a large and variable spectrum of clinical symptoms and anthropological traits (3, 4, 8, 22, 24, 25). Reports on the developmental and behavioural phenotype are scanty. Recent investigations suggest that the developmental abilities might have been regarded too pessimistic (2, 11, 15). The purpose of this paper is to show by a single case study that careful and systematic analysis of the physical and developmental phenotype may be based on a distinct methodology, thereby contributing to quantitative syndrome definition and proper parental counseling regarding the children's developmental potentials.

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PATIENT

The boy was born post term to young, healthy, non-consanguineous parents. Clinical suggestion of WHS was confirmed by chromosome analysis. Deletion 4p15.2–pter de novo was found. Additionally a XXY condition was present. Anthropological and developmental investigations were performed at the age of 1 $^{10}/_{12}$ years.

METHODS

PHYSICAL PHENOTYPE

A catalogue of well-defined traits was used for systematic collection of clinical symptoms and anthropological traits (20). Anamnestic data regarding preconceptional period, pregnancy, birth, neonatal period, developmental course and history of diseases were obtained from the parents and hospital records. A semi-standardised protocol was used for the assessment of rare anthropological traits in the skull, face, trunk and limbs (19). Facial measurements were performed from frontal and profile photographs quantifying seventeen traits by age related indices (21). On the basis of these data the child's trait list was set up by checking all informative catalogue features for presence or absence (5, 18).

DEVELOPMENTAL PHENOTYPE

In order to assess the developmental phenotype, the boy was observed during his interactive play with the therapist (L.A.) in an environment structured according to Montessori's method (1, 10, 12). She made contact, invited him to play, showed him how to use the material, supported him until the work was finished and helped to bring the material back to its place. A video record of the first sequence was analysed using the methodology of modern qualitative research (9, 16, 17):

1. capturing pictures moment by moment with computer assistance,
2. description what the child is doing in each moment,
3. structuring these descriptions in a protocol containing all observations,
4. interpreting these observations and coming to conclusions.

When focusing on the boy's developmental abilities and educational needs (14), we took advantage of Montessori's philosophy regarding the children's psychic and intellectual growth resulting from their interaction with the environment. The analysed sequence referred to an exercise of daily living (pouring semolina) designed to stimulate perception,

fine motor skills, repetition, and concentration. The material was a small tray with a funnel and two transparent bottles, one filled with semolina, the other empty. The activity lasted 17 minutes. The number of captured pictures was 771.

RESULTS

PHYSICAL PHENOTYPE

Clinical symptoms (n = 32)

Intrauterine growth retardation was observed during pregnancy. Delivery occurred by induced labour after 42 weeks. Birth weight was reduced (2700g, < p 10). The first cry was weak. Muscular hypotonia was present, leading to hypoactivity and difficulties in sucking and breathing. A newborn infection was treated. Later the boy had repeated urinary tract infections due to vesico-ureteral reflux. Because of permanent feeding difficulties his weight remained low (< p 10). Paediatric investigation revealed hypospadias, cryptorchism, and muscular hypotrophy. Myoclonic jerks occurred at the age of 3 months and were followed by seizures. Antiepileptic treatment was started at 16 months. Neurological investigation showed myoclonus, opisthotonos, and lack of extension reflexes. Cerebral computed tomography revealed hypoplasia of corpus callosum and delayed myelinisation. Ophthalmologic investigation showed signs of optic nerve atrophy (pale optic disks) and strabism. Laboratory investigations indicated hypoglobulinaemia. The boy's hypoactivity persisted. He expressed few mimics and held his mouth frequently open. Motor development was delayed, as well as closure of fontanels and dentition. At the time of investigation he could neither sit nor crawl and vocalised only few sounds. His motor activity was disturbed by numerous involuntary movements.

Anthropological traits (n = 46)

Forty-two craniofacial traits (Fig. 1) were recorded; ten of them were defined by measurements (marked bold):

Small head circumference (< p 10); flat occiput; prominent forehead with medial soft tissue swelling (haemangioma); high frontal hairline; prominent upper orbital arcs; round face; **low midface**; **broad intercanthal distance**; **narrow palpebral fissures**, down-turned on the right; laterally hypoplastic eyebrows; broad nose root; **long back of the nose**; broad, slightly down-turned tip of the nose; broad nasal septum; **inverted nasal plane**; **prominent upper jaw**; **short nasolabial distance**; broad philtrum with deep groove and prominent columns running into the nares; trapezoid shaped upper vermillion; **narrow mouth**

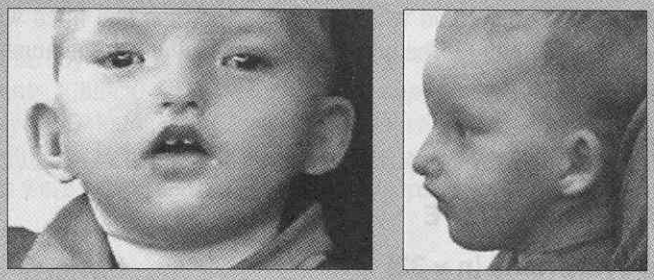

Figure 1:
Facial phenotype at the age of 1 10/12 years.

fissure; small, widely spaced teeth; high, cleft palate; receding lower lip; deep sulcus mentolabialis; **low chin**; protruding ears; short helix root; flat ascending helix; flat upper, prominent lower crus anthelicis with rectangular branching from the broad corpus; broad fossa triangularis; small lobulus.

Four anthropological traits were recorded on the trunk and limbs:

Broad intermamillary distance; small penis; distally tapering fingers; partial syndactyly of 2nd and 3rd toes.

DEVELOPMENTAL PHENOTYPE

Abilities (n = 44)

Motor/psychomotor abilities

The boy was able to sit with and without support, to extend his arms and hands towards objects or actions of interest, to follow moving objects with his eyes sometimes making corresponding arm movements, to turn his head and eyes at static objects of interest even when these were not located in front of him, to turn his head towards whispered phrases, to grasp objects of interest, to touch and move them, to near actively to persons or actions who attracted his interest and to retract from rapidly approaching objects that frightened him (n = 9).

Perception (Fig. 2)

The boy was able to observe actions presented to him and to notice the results explained to him by simple words when the work was completed. He perceived the quality of objects given to him by exploring them with his hands, but also with his mouth and nose while observing the therapist's face. He also perceived objects getting in touch with him and reacted to it by movements (n = 7).

Attention

The boy was able to focus his attention to objects or actions after the adult's friendly demand to do so. He could keep his attention to actions

After the therapist's repeated attempts to attract his attention he is starting to observe the semolina pouring.

He is looking at the empty bottle shown to him while the word « empty » is repeated several times.

Having received the empty bottle he is starting to explore it with his mouth while observing the therapist's face.

Figure 2: Examples for the boy's perception.

until they were completed, maintain it despite disturbances by the environment or distractions by own involuntary movements and restore it after temporary focusing on other objects or actions, after denial as demonstrated by crying or after involuntary movements. When paying full attention to an action, he was able to stop his involuntary movements (n = 8).

Social and communicative abilities

The boy could respond by eye contact to the invitation to play, to friendly demands to handle an object or to words of praise. He could establish eye contact with his mother for seeking assurance when facing a new experience. He could search for eye contact with the therapist, giving feedback to her when she had accomplished an interesting action. He was also looking for eye contact with other persons, including the camera, to share own observations or to ensure that his own actions were recognised. He was able to express his loss of interest in the play work by looking aside and staying passive in spite of friendly demands to continue and to express his unwillingness to do so by throwing things away (n = 9).

Emotional abilities

The boy could profit from his mother's body support when facing a new experience or unpleasant circumstances and actively searched it to

feel protected. He could also profit from her caress and whispering in difficult situations getting calmed in that way. He was able to express excitement after a new experience by stretching both hands and raising his left foot or opening his mouth. He could express pleasure by looking happy or smiling when having experienced success. He manifested anger by crying when feeling disturbed, and fright by looking unhappy or touching his head when new objects were brought close to him too rapidly (n = 6).

Own actions (Fig. 3)

The boy was able to join the therapist's actions spontaneously or after invitation. He was also able to undertake own logical actions required at a given step of the play work spontaneously or after invitation. Furthermore he was able to correct himself when having missed the target, e.g. when grasping an object (n = 5).

After the therapist's friendly invitation, he makes eye conact with her, opens his arms and joins the play work: leaning forward and looking at her he puts his right hand on the full bottle and keeps it there while pouring the semolina. His open left arm remains quiet.

After the repeated invitation to take the funnel out of the full bottle, he looks at it and starts grasping. Leaning forward, he encircles the funnel with both hands and draws it out. «Right!» the therapist confirms. He holds the funnel in both hands, elevates it to his face, closes his eyes and apparently smells the flavour of semolina.

Figure 3: Examples for the boy's ability to carry out own actions.

Needs

Following the analysis of abilities a number of needs were identified, which have to be satisfied by the environment to support the development of the boy's inherited pattern of psychic and intellectual growth including his motor functions:

Complex material to play. The boy should be invited to play with particular material obtained from his home environment to learn how objects are related to complex actions. Arranged on the basis of Montessori principles, exercises of daily living could for example involve simple and specific tasks, which he may already have observed to be done by the adults at home and which he therefore may wish to imitate. Such desired imitation is of intellectual nature because it is based on previous observations and acquired knowledge. By similar exercises his attention will further develop and his fine motor abilities will be trained.

Physical support. When working with such complex material, he needs physical support enabling him to achieve the given task, thereby making significant and age-related experiences in spite of his motor difficulties. He will learn that his own motor activities can have an aim. The boy has shown that he can repeat and improve movements by himself when the intended aim was not reached at the first attempt. Guided by his interest he will develop his motor skills in that way. Furthermore, the contact of different body parts with objects of interest will help him to develop physical self-awareness.

Verbal/non-verbal communication. The boy has also shown that he can listen and react to verbal communication. Normal speech understanding should be expected in spite of his limited speech production unless the opposite is proven. He needs an environment, where children and adults are speaking normally with him, supporting their own speech by gestures and mimics. Attention has to be paid to his non-verbal communication. His environment must react to it, provoke it by questions and friendly demands, expect his answers and repeat verbally what was understood. Going beyond the discussion of basal needs, he must be given the opportunity to develop his communicative abilities for more and more significant conversation out of simple dialogues.

DISCUSSION

PHYSICAL PHENOTYPE AND DIAGNOSTIC CRITERIA

Although the phenotype is leading to diagnosis, widely recognised diagnostic criteria are missing for WHS. Published cases are simply

based on similarities to previous descriptions and confirmed by cytogenetic findings (3, 4, 24). Available reviews indicate a variety of clinical symptoms and anthropological traits (4, 8, 24, 25), which are not based on systematic data acquisition. Today, as cases with sub-microscopic 4p deletions are known and WHS genes are being searched for (26, 27), more exact knowledge seems to be necessary. Significant links to different extents of monosomy 4p can only be performed when the phenotypes are defined by quantitative criteria. The physical phenotype of the presented child, which was characterised by 78 features, can contribute to that knowledge. Further systematic work on children with monosomy 4p will lead to an objective phenotype definition of this chromosomal syndrome.

DEVELOPMENTAL POTENTIAL AND PARENTAL COUNSELING

Following cytogenetic diagnosis, parental counseling about the children's developmental prognosis should be based on an accurate knowledge on this syndrome-specific phenotype. However, little is known what is normal for children with WHS. Comparing them to normal populations must be misleading (16). Anticipating a «wrong» development will stigmatise them. Negative prophecies will distract parents and health care professionals from realising their genuine abilities and developmental potentials. Furthermore, parents' intuitive capacity to catch their psycho mental signals will be limited by their unresolved grieve over the loss of their imagined children who had normal chromosomes. Professionals being asked for advice should switch from focusing on physical limitations to supporting parents regarding their children's psycho mental growth and health.

Analysis of the developmental phenotype in the presented boy revealed a number of 44 abilities referring to all major aspects of psycho mental functioning. Despite his motor restrictions and an untrained concentration, he was able to perceive new and interesting things, persons and actions in his environment. He could interact with them, showed emotions and performed own intelligent actions. Recognising these abilities let us formulate his needs: He should be assisted and empowered to take part in all events of daily life. Particular use should be made of his speech understanding and non-verbal communication. Due to motor restrictions, he needs direct physical support to handle things and solve tasks, which are interesting for his age. These needs should be satisfied to prevent psychomotor and mental disability, which may arise secondarily to his chromosomal syndrome.

Further case studies will contribute to a better understanding of the developmental phenotype of WHS, making it easier for genetic counselors to correctly predict their real prognosis. Health care professionals should look more optimistic upon their potentials and design pro-

grammes able to assist parents to support their children and to educate them adequately in spite of their chromosomal syndrome.

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