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CASE REPORT

M. von Aster
M. Zachmann
D. Brandeis
G. Wohlrab
M. Richner
H.-C. Steinhausen

Psychiatric, neuropediatric, and neuropsychological symptoms in a case of hypomelanosis of Ito

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M. Aster (✉) · M. Richner · D. Brandeis
H.-C. Steinhausen
Departement of Child
and Adolescent Psychiatry
University of Zurich
Freiestr. 15
CH-8028 Zurich
Switzerland

M. Zachmann · G. Wohlrab
Department of Pediatrics
University of Zurich
Steinwiesstr. 75
CH-8032 Zurich
Switzerland

Abstract This case report presents a thirteen year-old boy who was diagnosed as having Hypomelanosis of Ito. The developmental history includes severe failure to thrive, and moderate atypical autism as well as diverse clinical and neuropsychological symptoms are present. The pattern of neuropsychological functioning, which can be partially related to the neurophysiological findings, is discussed within the context of existing neuropsychological theories about autistic disorders.

Key words Hypomelanosis of Ito – failure to thrive – autistic disorders – Nonverbal Learning Disability syndrome (NLD) – neuropsychology

Introduction

Hypomelanosis of Ito (HI) is a congenital neurocutaneous syndrome characterised by sharply circumscribed hypopigmented streaks, spots, and whorls that are usually distributed along the lines of Blaschko on the trunk and occasionally on the extremities and the face. Symptoms of central nervous system disorder seem to be present in about half of the published cases, especially epilepsy and mental and psychomotor retardation. Ophtalmologic abnormalities (myopia, strabism, retinal dysplasia), skeletal abnormalities (micro- or macrocephaly, facial and extremity asymmetries), and sleep disorders are often associated with HI. In 60 out of 115 reported cases, abnormal chromosome constitutions were present. Most of them were mosaics for aneuploidy or unbalanced translocations (21).

HI is considered to be one of 24 medical disorders that are possibly related to autism or autistic-like conditions (6, 7).

As with other medical disorders, the reported frequencies of associations of HI with autism differ widely. This may be due to differences in diagnostic instruments and criteria. Zappella (27) found autistic symptoms in 64% of HI cases, whereas in the study by Pascual-Castroviego et al. (16), only 4 out of 35 patients (11%) with HI were autistic. Zappella (27) hypothesized that a special neuroendocrine dysfunction might be responsible for the autistic symptoms in HI. He refers to a biochemical model proposed by Chamberlain and Herman (4) that links dysfunctions in brain melatonin secretion, proopiomelanocortin peptides, and serotonin to both autism and depigmentation of the skin (and other associated symptoms like sleep disorders and reduced sensitivity to painful stimuli).

The following case report illustrates a diversity of psychiatric and neuropediatric symptoms and their possible link to HI and other medical conditions that were diagnosed during early and later childhood development of the patient.

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Case report

Referral

L.B. was admitted to the child psychiatric inpatient unit when he was 13 years old. He was referred by his child psychotherapist who saw him almost daily during the last weeks before hospitalisation because of increasing aggressive and disruptive behaviour with verbal and physical attacks, especially against his mother and his younger brother. In addition to psychotherapy, he had been treated by his pediatrician with methylphenidate since the age of 11 years (50 mg per day) with only minor therapeutic effects. He attended a private school with a regular curriculum but a very small class size.

History

L.B. came from a family with no specific psychiatric or medical history. None of the siblings (one sister +3, one brother –9 years) had any developmental problems or severe medical disorders to date. The family first lived in the USA and then moved to Switzerland when L.B. was five years old. His native language is English. He aquired German as a second language from the age of five.

During pregnancy L.B.'s mother often suffered from severe headaches that were treated with Tylenol. Intrauterine growth retardation was diagnosed. L.B. was born after 37 weeks gestation and was small for date (1800 g). Neonatal screening for congenital disorders of metabolism (i.e., PKU, galactosemia) were normal. During the first year of life there was a severe failure to thrive with vomiting and excessive sweating. Weight and height were below the 3rd percentile, and head circumference was in the 10th percentile. Thyroid functioning (T3, T4, and TSH) was within the normal range. Extensive medical and laboratory examinations did not reveal any organic cause for the failure to thrive syndrome.

Otitis media first occurred at the age of two months and recurred frequently up to school age with a resulting hearing impairment in the right ear. This impairment remitted after an adenotomy and paracentesis when the patient was 9 years old. At the age of seven months, repetitive sudden head nodding accompanied by blinking of the eyes was observed. Findings from EEG and CCT were normal. The peripheral blood caryotype was 46 XY.

Because of the above-mentioned and some other health problems, L.B. was hospitalized several times during the first years of life. HI was diagnosed before age two years because of the typical skin depigmentation, located at the right side of his back, as well as his right arm and leg. He was noted to have delayed motor and speech development (unaided walking at 3 years, a few first words at 2.5 years, first sentences at 4 years). However, at the age of 12 months it was noted that gross motor development appeared delayed, whereas other developmental functions were within the age-appropriate range (Bailey Scales and Denver Developmental Screening Test). The mother reported that already at a very early age, L.B. had disliked and refused physical contact (i.e., caressing, being held in the arms), and that he did not show much interest in social interaction and symbolic play.

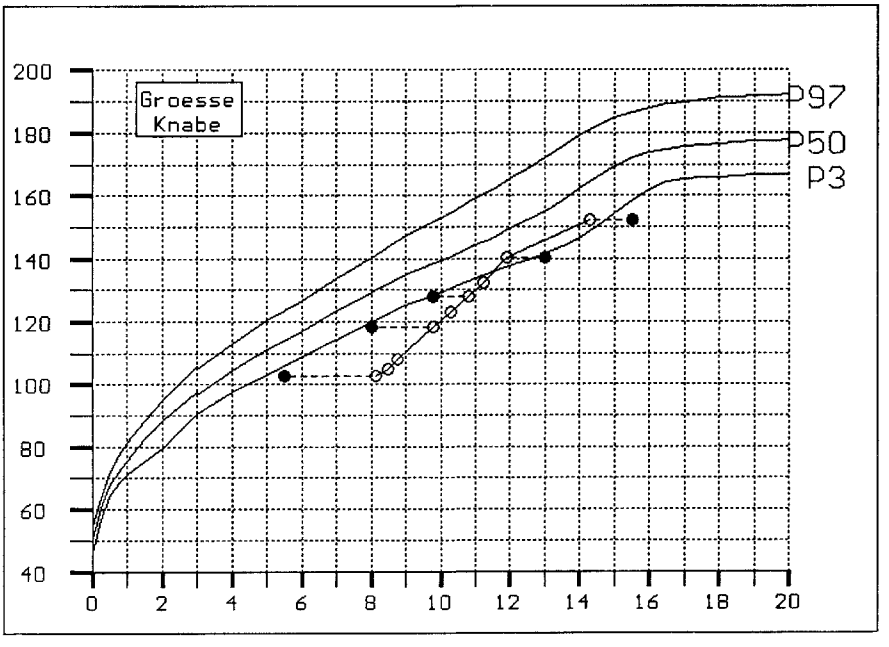

Fig. 1 Growth curve of the patient during treatment with human growth hormone (open circles: height for chronologic age, full circles: height for bone age)

L.B. entered kindergarten in Switzerland at the age of 5 years. Extensive psychological and medical assessment showed a marked language (English) and psychomotor developmental delay but a normal nonverbal intelligence score. He showed only little interest in personal communication and social interaction, and he manifested moderate hyperactivity and distractability. L.B. was admitted to a special school for children with speech and language problems and was referred to psychomotor and speech therapy.

Since the age of 8.5 years, L.B. has been treated with human growth hormone (hGH), although GH-secretion responded normally to stimuli. At the start of treatment, there was marked short statue with a height of 108 cm (–4.4 SD) and delayed bone maturation (chronologic age 8.1 years, bone age Greulich and Pyle 5.5, Tanner et al. 5.8 years). Head circumference was normal (75. percentile). On treatment with recombinant hGH (4 IU daily, subcutaneously) there was impressive catch-up growth (Fig.1), and height at age 14.3 years was normal (–1.6 SD). However, also bone maturation was accelerated on treatment and was even slightly advanced at age 14.3 years (Greulich and Pyle 15.5, Tanner et al. 16.1 years). In spite of the impressive catch-up growth, the height prediction did not increase and was only 156,5 cm (Bayley and Pinneau) at age 14.3 years.

Beginning at 9 to 10 years teachers and parents noted increasing behavioral problems that included aggressive and disruptive behavior, restlessness, sleep problems (failure to fall asleep), tendency for perseverating behavior, and cognitive rigidity. Psychological assessment at the age of 12 years showed an overall intelligence score of 77 (Kaufmann Assessment Battery for Children, KABC, German test version) with marked deficits in 'block-design' and verbal subtests.

Psychiatric, neuropediatric, and neuropsychological findings

Compared with his peers, the small but wiry boy was immediately perceived as being very deviant in the areas of social communication and interaction. He rarely engaged in eye-to-eye contact, his affect (smiling, laughing, anger, and distress) as well as verbal comments often did not seem to be appropriate to the social or situational context. He was obsessively concerned with sports, especially basketball and soccer, and he knew the names of all the players of well known teams as well as all of the results of the weekly games. When playing basketball or soccer with other children, he was very seriously engaged and often criticized other boys when he thought they made mistakes. In fact, compared with the other children, he had very limited motor skills, not only due to his small statue but also to his general poor motor coordination. His criticism was not taken seriously by his peers, who regarded his behaviour as somewhat bizarre, which he did not realize. It seemed that he felt himself to be the captain of the team, but he was rather playing alone within the team, more or less isolated from his team mates. His teacher and other educators often reported that he could not perceive his own physical limitations and that he seemed insensitive to painful stimuli (injuries) and cold temperature.

With time, the aggressive and disruptive behaviour generally decreased and usually only occurred when he was confronted with unexpected changes in the course of daily events or with noisy, confusing, or new social situations. He was now often observed to fall asleep immediately upon going to bed, both after lunch and at bedtime. It was also observed that he sometimes had difficulties in localising acoustic stimuli; he often looked in the opposite direction when he was called. Furthermore, he had difficulties in memorizing social and contextual events. For instance, he was very confused when he came back from a short vacation with his parents, because he noticed that a girl was missing, who was discharged from the inpatient unit. He could not remember that he had participated in a farewell party for this girl before he left for holidays.

L.B. learned to play the guitar quite well and was perceived to have some talent for music. At school, his reading skills were poor but quite more advanced than his spelling abilities. Fine graphomotor abilities, language perception and performance, and especially mathematical skills were also poor. He could manage some simple multiplication tables but was unable to grasp mathematical concepts. He had severe difficulties in solving arithmetical problems and also had difficulties with simple addition and subtraction and in estimating quantities. In addition, he tended to persevere in false strategies, even if he was corrected several times. During lessons, he was sometimes perceived as being mentally absent.

It was decided to gradually reduce and finally eliminate methylphenidate. When this was told to him, he was very confused and distressed about this change in his daily rhythm of medication, which he obsessively controlled by frequently checking the time and demanding the application precisely as scheduled. There were no pronounced behavior changes after stopping medication. L.B. was slightly more active and distractable, but also seemed less rigid in his emotional and cognitive functioning.

L.B. fulfilled the criteria for atypical autism according to ICD-10 research criteria: impaired development of language, impaired reciprocal social interaction and symbolic play before the age of three years; five symptoms of abnormal social interaction, communica-

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tion, and specific pattern of behavior, interests and activities.

On the Child Behavior Checklist (1) he had a borderline score on the 'withdrawal' scale (t-score=69, according to Swiss norms (20) and on the 'social problem' scale (t=69), and he had abnormal scores on the 'thought problem' (t=75) and the 'attention problem' scale (t=78). On the Childhood Autism Rating Scale (18) he scored 33, indicating moderate autism.

Neuropsychological assessment revealed the following results. A full scale IQ of 72 (verbal IQ 61, performance IQ 89) was assessed with the German version of the WISC-R. Performance was especially weak in the subtests 'information' (2. percentile), 'arithmetic' (5. percentile), 'similarity' (2. percentile), and 'vocabulary' (0.5. percentile) as well as in 'block design' (5. percentile) and 'object assembly' (1. percentile). He showed good results on 'comprehension' (37. percentile), 'number-symbol test' (37. percentile), 'picture completion' (91. percentile), and 'picture arrangement' (75. percentile). Performance was no better on the verbal subtests when presented in English (VIQ = 59). However, on the Token Test (TT), measuring language comprehension (15) L.B. attained differing results, depending on whether the test items were presented to him in German or in English. His performance in the English version was better and was exactly at the cut-off score for aphasic children, as defined by Gutbrod and Michel (10). With the German version he scored clearly within the group of aphasic children. He scored at the 16^{th} to 25^{th} percentile for school grade on the reading test (Zürcher Lese-Test, ZLT). However, he is two years behind in school.

In a task that requires the discrimination of facial expressions of emotional states (9) he could only differentiate between extreme items such as 'happiness' and 'anger', but he failed in differentiating items such as 'anger' and 'unfriendliness' or 'contentedness' and 'happiness'. On the Rivermead Behavioral Memory Test for Children (26) he had relatively normal results in the area of immediate memory functions but had difficulties in tasks requiring delayed response. He needed intensive prompting, especially if he had to remember non-verbal (hidden belonging) or contextual (appointment) material.

Laboratory findings

In order to prove possible dysfunctions in brain melatonin, the principal metabolite of melatonin (6-sulfatoxymelatonin) was measured in urine. The circadian rhythm was normal but the total value for 24 hours was slightly elevated (+1.5 sd). MRI (T2) showed a lesion located at the uncus and corpus amygdaloideum of the right hemisphere, which is suspected as being a tumor or cystic malformation.

The standard EEG as well as long-term monitoring showed age-appropriate activity and regular sleep stages. Only very few signs typical for epilepsy were found, but they were regarded as being of no clinical significance.

Brain mapping of EEG and event-related potentials (ERPs) employed the 32 channel montage and the recording parameters described previously (3). Given the lack of normative ERP data for our language and attention test in L.B.'s age range, we only discuss deviations which are related to previous work and reflect deviations of at least 2 SD's from the mean of the younger control groups available for comparison.

Visual inspection of the resting EEG (eyes closed, for 3 min.) showed several epochs of right alpha slowing and right > left asymmetries exceeding 50%. Magnitude spectra computed for artefact-free 2 sec. epochs (0.5 Hz resolution) showed this asymmetry most clearly at O2 vs. O1. It was pronounced for the 9.5 Hz and the 10 Hz band but not for the 10.5 Hz band.

In the reading task, simple sentence stems selected for having a high-probability colour ending (i.e. the sky is...) were terminated randomly by semantically correct or incorrect endings. These setences were shown word by word on a monitor. L.B. had to read them silently. After some endings he was prompted to verify whether the previous sentence had been correct or incorrect. L.B. classified 86% of the sentences correctly, even though words were presented too briefly to permit letter-by-letter reading (1 word/ 570ms, on-time 250 ms, off-time 220 ms). L.B.'s performance was clearly above chance performance (50%). It was also above the performance of younger dyslexic children (79% at 11.6 years) but below the performance of the nearly 3 years younger control group (91% at 11.2 years). The ERP maps evoked by terminal words indicated a normal response to semantic incongruity (symmetric parieto-occipital N400 negativity) which was neither delayed nor attenuated as had been found in the dyslexic group (3). The word-evoked VEPs of L.B. showed a reduced left-occipital amplitude in the initial P100 phase (80–110 ms), similar to the P100 reduction found in the dyslexic group. Overall the reading test results are consistent with a moderate receptive language impairment. The brain mapping results (EEG and word evoked VEPs) provide some evidence that a left posterior dysfunction could contribute to L.B.'s reading problems as previously reported for dyslexic children.

In the A-X version of the Continuous Performance Test (24) a sequence of letters was presented on the monitor (1/1.65 sec), and L.B. had to respond to the letter X preceded by the letter A (10% probability). He needed extended practice but then performed well without being particularly fast (100% hits, 2 false alarms

over 400 trials, target reaction time 470 ms). The ERP maps showed clear differential processing for relevant and irrelevant items. His early P300/CNV-response to the relevant cues and targets was of normal amplitude and latency compared to a younger control group (10.9 years), suggesting normal early orienting (24). The amplitude reduction and the delay to cues present for an ADD group (11.2 years) was not seen. The posterior positive and prefrontally negative topography was normal; the less occipital distribution and the reduced duration compared to the younger control group is also seen in other older children. After cued targets, the basic P300 was again normal, except for an early right > left asymmetry at parietal sites. Only the pattern at right parietal sites is reminiscent to the earlier P300 after cued targets reported by Townsend and Courchesne (1994), but the asymmetry and the lack of fast reaction times argue against a functional similarity.

Discussion

In the present case report HI is associated with autistic symptoms, as was initially described in three cases reported by Akefeldt and Gillberg (2). In summary, the main three symptoms of early onset autism – impairment of language development, social interaction, and symbolic play – were present in L.B. before the age of three years, according to his mother's report. In the course of development he reached a relatively high functional level in the areas of social-adaptive behaviour and cognitive as well as academic skills. Deficits persisted in the areas of reciprocal social interaction and communication abilities, which has been conceptualized as being a specific disorder of empathy (8). L.B. ist mentally retarded, as are about 50% of the HI patients who have been documented. Cognitive functions are not homogenously low but show some specific strengths and weaknesses. However, the neuropsychological findings are not entirely consistent with the profile of strengths and weaknesses that are supposed to be typical for autism.

For example, although L.B.'s verbal abilities were poorer than his performance skills on the WISC, he did not show the typical profile of good results in 'block design' and 'object assembly' and poor results in 'comprehension' and 'picture arrangement', as described, for example, by Frith (5). In contrast, L.B. showed the reverse pattern. His very poor results in 'block design' and 'object assembly', indicating deficits in visual-spatial abilities and in nonverbal concept formation, partially resemble the neuropsychological pattern of Nonverbal Learning Disability syndrome (NLD), which was defined by Rourke (17). NLD has recently been described as being typical of Asperger Syndrome (AS) and as discriminating AS from high functioning autism (11). L.B. also showed other deficits in neuropsychological and cognitive areas that are typical of NLD (i.e., fine and gross motor skills, novel material, mathematics). Nevertheless, he did not meet the full set of NLD-defining criteria and, more specifically, he did not show the typical assets in auditory-verbal functions as well as in reading and spelling skills. However, it has to be mentioned here that, although L.B. manifested significant delay in language development, which contributes to the diagnoses of autism, it is not clear whether or not his language delay is of purely or 'classical' autistic origin. Several other factors might possibly have affected his receptive and expressive language development and the development of reading and spelling abilities. For example, the recurring otitis media with hearing impairment, bilingualism, as well as the low birth weight and the severe failure to thrive that are recorded in his developmental history might also be contributing factors (19). It should be noted here that, to our knowledge, failure to thrive has never been described before as being associated with HI.

ERP research suggests that children with dyslexia may have deviant visual and cognitive components of the ERPs, but the actual deviations have been inconsistent (reviewed in Brandeis et al. (3)). In one of our own studies (3), we found both visual and semantic ERP anomalies. In the resting EEG, dyslexics had a more right-lateralized topography of the spectral alpha band than the control subjects (14).

The literature on visual ERPs in autistics suggests that P300 amplitudes are typically reduced (23). However, Townsend and Courchesne (22) found P300s of normal amplitude to cued targets in autistics, and faster reaction times and earlier P300 latencies than controls in a subgroup of autistics with parietal damage.

Overall, brain mapping provided no direct evidence of either general or localized dysfuction, which is constistent with the clinical EEG and, indeed, even indicates intact basic semantic and normal attentional processing. The posterior asymmetries found for the early phase of the word-evoked P100 and for the alpha at rest are partly reminiscent of findings with reading-impaired children and may suggest a functional impairment of left posterior areas. The P300 abnormalities described for autistics could not be observed in our CPT cueing task.

It cannot be decided to what extent L.B.'s symptoms and dysfunctions are related to the cystic or tumorous lesion found in the MRI. It seems probable that his difficulties in localizing acustic stimuli and in memorizing nonverbal and contextual material can be attributed to his right-sided temporal lesion (12). However, lesions in this area have often been said to cause autistic symptoms and the frequently associated psychomotor epilepsy as well (for a review see Gillberg and Coleman (7)). Although EEG long-term recording did not show

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significant sharp-wave activity, it cannot be denied that the severe aggressive disruptions that lead to L.B.'s hospitalization and the occasionally observed states of mentally absence may have been due to clinical or subclinical seizures. Stimulant medication might have caused an increased vulnerability for seizures. The mentioned symptoms decreased after the gradual reduction and elimination of medication.

It might be of particular interest to further investigate the role of brain melatonin in the subgroup of patients with autistic symptoms and HI, as was proposed by Zappella (27). L.B. showed slightly elevated values for 6-sulfatoxymelatonin, the principal metabolite of melatonin, which might perhaps not only provide some explanation for the observed sleep irregularities but also for the autistic and cutaneous symptoms in general.

In conclusion, we found different psychiatric and neuropsychological symptoms in L.B. that can be related to left- as well as right-sided lesions and dysfunctions. However, these findings are difficult to explain within the existing empirical and theoretical frameworks concerning specific autistic dysfunctions.

Although L.B. does not meet the AS-defining criteria because of the 'classical' onset criteria and impaired language development in his own history, he does show a neuropsychological pattern of assets and deficits that corresponds partially to NLD, which in turn has been said to be typical for AS but not for 'classical' (high functioning) autism. NLD has been conceptualized as a dysfunction of the right hemisphere, and there is empirical support that children with developmental mathematical disorders and NLD develope socio-emotional problems and internalising psychopathology. From a neuropsychological point of view these difficulties can also be explained within the concept of empathy dysfunction. For example, Loveland et al. (13) could demonstrate that children with NLD are likely to misinterprete nonverbal aspects of social interaction such as affect, motivation, and intentions (for a review see von Aster, 1994).

Gillberg and Coleman (6) suggest that disorder of empathy possibly emerge from dysfunctions of the left, the right, or of both hemispheres. A neuropsychological perspective might be enlightening that would help to formulate a hypothesis of information processing in social interaction and communication by defining different representational brain-modules for linguistic, paralinguistic, and nonverbal material. These would most probably be located in both hemispheres, connected to each other by transcoding pathways, and activated according to situational needs. Disorders in a specific information processing system may result from a great diversity of possible dysfunctions and disconnections that lead to impaired abilities to behave reciprocally in social interaction.

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