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Fetal alcohol syndrome: amino acid pattern

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A study of the serum amino acid concentrations in 6 children with the fetal alcohol syndrome revealed significant changes in their pattern, i.e. a decrease in hydroxyproline and proline (indicating disorders in skeletal development) and an increase especially in the alanine, leucine, isoleucine and tyrosine levels (indicating probably a damage to CNS development).

It is well established that alcohol is a teratogenic factor and that its abuse by mothers during gestation may lead to delivery of a defective child. Confirmatory evidence in that respect has been provided by detailed clinical and experimental studies published in many countries during the past 10 years, ever since a correct description of the fetal alcohol syndrome (FAS) had been given [3, 4].

The result of the intrauterine effect of alcohol is a defective somatic and mental development. The mental retardation is ascribed to structural changes in the brain produced during embryogenesis. Clarren et al. [1] demonstrated disorders in migration of neuronal and glial elements in the brain at autopsy of 4 children born to chronic alcoholic mothers. During the late fetal period alcohol is said to cause changes in the biochemism of the brain which result in behavioural disorders of the child during the postnatal period [7, 8]. Ellis and Krsiak [2] found in young rats fed with alcohol a low serotonin concentration in the brain. These young rats showed behavioural disorders manifesting with increased aggressivity, increased locomotor activity and decreased learning ability. Véghelyi et al [9] studied the question why some heavy drinkers give birth to healthy offspring while others who drink much less give birth to children with FAS. These authors could show that an involvement of the human fetus occurs in those women in whom after the intake of alcohol the level of acetaldehyde rises above 40 μmol [9, 10]. The mechanism of development of mental disorders in children with FAS is still obscure.

Involvement of the child's organism in FAS is of a general nature. Not only development of the brain is affected but also the growth and development of the skeleton, and this may justify the conclusion that in FAS a disturbance of the whole metabolism occurs. In the present study an attempt has been made to clarify these disorders by determination of the amino acid spectrum in the blood serum of children with FAS.

Reports of Cases

Of a total of 24 children with FAS, born to 12 alcoholic mothers and followed-up since 1978, and in 6 children 12 to 36 months of age, the serum amino acids have been studied by chromatography on ion exchangers (automatic amino acid analyser AAA8881 Mikrotechna, Prague).

Psychological examination was repeatedly carried out in all the children, up to 3 years of age by the method of Brunet–Lezine (DQ), and above 3 years of age by the method of Terman–Merill (IQ). The electrolyte household and liver function tests showed normal values and chromosomal examinations revealed a normal karyotype in every child. The investigated children showed the following manifestations of FAS.

Patient 1. B. Z., a girl born in 1976 was the first child of a 23-year-old mother who since more than 3 years and throughout the entire course of the pregnancy consumed a daily mean of 150 g of absolute alcohol. The child was born without complications, with a birth-weight of 1500 g, length 42 cm. Apgar score 10. She showed since birth an increased irritability, tremor of the extremities, and weak sucking. At the age of 3 years her weight was only 9500 g and her height, 90 cm. Both values were under the 3rd percentile and the head circumference was 46 cm (-1 SD). She had generalized hypotonia, hypertelorism, indistinct philtrum, gothic palate; fine light hair, hypoplastic slowly growing nails, slight arachnodactyly on the hands, hypoplastic labia maiora with a moderate mental retardation (IQ = 80) and conspicuous hyperactivity. The blood amino acid spectrum showed changes (Table I).

At 5 years of age, growth was below the 10th percentile, the peculiar appearance of the face persisted. The girl is mentally retarded, unconcentrated, jittery, especially failing in manual skills.

In 1979, the mother at 40 weeks gestation gave birth to a second child. The birth weight was 2100 g, the length 48 cm. At 3 years of age, the girl had cranio-facial dysmorphism with microcephaly (head circumference 44 cm = −3 SD). The growth values were under the 3rd percentile, the IQ was repeatedly around 50.

Patient 2. The male patient Ch. M. was born in 1976 as the eleventh child of a 36-year-old chronic alcoholic mother with 6 years history of alcohol abuse. During her last gestation she consumed a daily mean of 180 g, of absolute alcohol. The child was delivered without complications, with 2250 g weight and 44 cm length. The gestational time was not known. The 1 and 5 min Apgar score was 7 and 9, respectively. There were signs of immaturity.

On admission, at 5 months of age, the weight was 3330 g, the length 47 cm, psychomotor development was retarded, the developmental quotient DQ = 50. The child had an anomalous appearance, antimongoloid slant

of palpebral fissures, ptosis of right eyelid, strabismus, hypoplastic philtrum, thin upper vermilion border, gothic palate, strikingly low-set ears, fine light hair, spoonlike deformation of toe-nails, clinodactyly of both fifth fingers, hypospadias and fovea coccygea. X-rays showed a considerably retarded ossification, microphalangia of the toes on both feet.

Growth was always under the 3rd percentile, at 12 months of age the weight was 5000 g, at 24 months 6000 g, with 74 cm length, at 4 years of age it was 10 kg with 87 cm length. Psychomotor development was retarded, at 4 years of age the IQ was 50. The amino acid levels at 3 years of age are given in Table I.

On examining the family in 1978, we found that it consisted of two different groups of children. The first 8 siblings were born at term with a birth weight above 3000 g, they had dark hair and developed well both somatically and mentally. The three younger siblings born between 1973 and 1976 were small-for-dates, had light hair, delayed psychomotor development and growth deficiency. These three children were diagnosed as having FAS.

Patient 3. P. V. a girl, was born in 1979 as the second child of a 23-year-old mother with a 5 year history of alcoholism. She consumed a daily mean of 120 g of absolute alcohol. Delivery was without complications, birth-weight 2130 g, length 43 cm, estimated gestational age was 33 weeks. At 6 months the baby had severe psychomotor retardation, hypotonicity, cranio-facial dysmorphism, nail hypoplasia, growth retardation. At 6 months she weighed 4500 g, at 12 months 7100 g, at 18 months 8200 g, with 71 cm length and a head circumference of 44 cm (−1 SD), values under the 3rd percentile.

The amino acids at 18 months are given in Table I. At 2 years of age the child was severely underdeveloped, jittery, could not yet walk, her verbalization was unintelligible.

The first sibling, a girl born in 1977 with 2300 g and 46 cm length was raised by the grandparents. According to their information the child is severely underdeveloped, somewhat jittery, with retarded psychomotor development.

Patient 4. L. M., a boy born in 1978 was the third child of a 30-year-old mother with an 8 year history of alcohol abuse who up to the 4th month of gestation drank a daily mean of 150 g of absolute alcohol. After the gravidity had been confirmed she restricted somewhat her alcohol intake. Delivery at 38 weeks gestation, birthweight 2600 g, length 47 cm, Apgar score 10. At 8 months of age, the child had marked muscle hypotonia, his weight was 7900 g, length 70 cm, head circumference 43 cm. The facial characteristics were a hypoplastic nasal bridge, anteverted nostrils, short palpebral fissures, low-set ears. He had a ventricular septal defect. At 12 months the weight was 8300 g, the length 68 cm, corresponding to the 3rd percentile. He began to stand up

TABLE I

Serum amino acid concentrations (μmol/l)

	Cys OH	Tau	Asp	Hyp	Thr	Asn	Glu	Gln	Pro	Gly	Ala	Cit
Normal	0–20	14–215	0–17	32	114–335	45	20–106	537–888	106–277	223–509	235–409	0–28
B. Z.	0	163	10	*0*	186	2	85	385	*73*	195	**617**	0
Ch. M.	0	26	0	*0*	113	0	**201**	**934**	*14*	274	**690**	0
P. V.	0	71	**34**	*2*	201	13	72	541	*11*	**511**	**703**	4
L. M.	0	**286**	**21**	*0*	158	33	101	856	*0*	304	102	0
D. S.	14	209	2	*0*	171	41	**651**	639	*42*	353	**762**	0
H. M.	0	201	**53**	*0*	207	33	**122**	358	*16*	241	**770**	0
Mean values	2	159	**20**	*0*	173	20	**205**	619	*26*	313	**607**	0

Italics: decreased value
Bold face: increased value

at 2 years of age. X-rays revealed kyphosis, thoracic asymmetry, and other changes. For the blood amino acid values see Table I.

The first sibling, a girl born in 1967 with 2900 g and 48 cm length, is healthy with a normal appearance and intelligence. The second sibling, a boy born in 1976 has already the typical characteristics of FAS: a birth weight of 2100 g, length 44 cm, marked craniofacial dysmorphism with low-set ears, a heart defect, pigeon breast, clinodactyly of the fifth finger, camptodactyly on right hand, a cavernous haemangioma, fovea coccygea, etc. At 5 years of age his growth remains below the 3rd percentile, mental debility and hyperactivity. Throughout this pregnancy, the mother drank a daily mean of 180 g of absolute alcohol.

Patient 5. D. S., a boy was born in 1978 as the fourth child of a 37-year-old mother with an 8 year history of alcoholism. During this pregnancy she consumed a daily mean of 150 g of absolute alcohol. Delivery from breech presentation, birth-weight 1850 g, length 47 cm. At birth, the infant showed slight signs of immaturity, the Apgar score was 10. He had short palpebral fissures, a large nasal bridge, a long, flat philtrum, a thin vermilion border, low-set ears, nail hypoplasia, retention of testicles, scrotal hernia, generalized hypotonia and deformed lower extremities.

At 12 months of age the weight was 6300 g, at 2 years 8800 g with 77 cm length, values below the 3rd percentile. Defective psychomotor development, DQ = 60–70. The serum amino acids showed abnormal values (see Table I).

The first two siblings are normal and healthy. The third sibling, a girl, was born at term in 1972 from an uncomplicated gestation, with a birth-

in children with FAS

Val	1/2 Cys	Met	Ile	Leu	Tyr	Phe	β-Ala	Orn	Lys	His	Arg	Ser
80–245	70–168	9–41	26–52	47–109	41–99	41–110	0–14	49–151	114–268	48–114	21–87	94–242
443	70	**63**	**113**	6	92	94	0	34	100	41	11	195
301	91	**50**	**125**	**147**	59	8	0	11	256	54	15	20
453	100	**54**	**78**	**204**	**159**	20	0	23	**285**	16	20	193
109	20	**71**	**107**	**121**	**101**	51	0	8	103	88	**101**	201
356	21	**77**	**63**	**225**	**128**	87	0	91	**283**	48	**125**	224
428	42	**68**	**153**	**258**	**191**	9	0	143	**285**	**115**	**105**	**254**
348	57	**64**	**90**	**160**	**122**	45	0	52	219	60	63	181

weight of 2400 g and 45 cm length. At 7 years of age, she was mentally backward, she had mutism, encopresis and enuresis. Her growth persisted under the 3rd percentile.

In 1980 a fifth child was born, with 1600 g birth-weight and 41 cm length and the characteristics of FAS with the same cranio-facial dysmorphims as his older brother D. S., and some other changes. His growth persists under the 3rd percentile, he is hyperactive and mentally deficient with a DQ of 50.

Patient 6. H. M., a boy born in 1978 was the second child of a 33-year-old chronic alcoholic mother. Since 6 years and also during her pregnancy she consumed a daily mean of 240 g of absolute alcohol. The baby's birth weight was 3250 g, his length, 50 cm. Since birth the infant has shown increased irritability and disorders in food intake. To unusual situations he reacted with increased tremor up to convulsions of the upper extremities. He has a conspicuous epicanthus, strabismus, hypoplastic philtrum, gothic palate, heart defect, umbilical hernia, and generalized hypotonia. He has a slight cerebellar dysfunction and began to walk at 2 years of age. For the amino acid values see Table I. At 4 years of age, growth was at the 10th percentile, the IQ was 55 with severe psychomotor instability.

The first child, born in 1971, is somatically healthy and mentally well-developed.

Results

Table I shows the values for the individual amino acids. The first line contains the levels obtained in matched controls to facilitate comparison with those of the affected children.

From Table I it is evident that abnormal levels occurred in every examined child. Proline and hydroxyproline were considerably decreased to approximately 1/10 of the normal while the levels of alanine, valine, methionine and isoleucine were increased. The concentration of leucine was increased in 5 children, that of tyrosine in 4 children, both by 50–100%. It was not possible to find a relationship between these values and the clinical symptoms.

Discussion

Decreased hydroxyproline and proline values are usually associated with disturbances of growth and development of the supporting apparatus. This might be due to a disturbance of collagen and elastin metabolism. Still, the cause of the alteration is not clear and some disturbance in liver metabolism induced by alcohol might be assumed. Also, the increased concentration of tyrosine, leucine and isoleucine has a negative effect on development of the central nervous system and this damage together with the morphological changes, may elicit the neuropsychic symptoms in children with FAS. Further studies are, however, required to clarify the meaning of the affected amino acid pattern and also its eventual use in diagnostics.

References

1. Clarren SK, Alvord EC, Sumi SM, Streissguth AP, Smith DW: Brain malformations related to prenatal exposure to ethanol. J Pediatr 92:64, 1978
2. Ellis J, Kršiak M, Pöschlová N: Effect of alcohol given at different periods of gestation on brain serotonin in offspring. Activ Nerv Sup 20:287, 1978
3. Jones KL, Smith DW, Ulleland C, Streissguth AP: Pattern of malformation in offspring of chronic alcoholic mothers. Lancet 2:1267, 1973
4. Jones KL, Smith DW: Recognition of the fetal alcohol syndrome in early infancy. Lancet 2:999, 1973
5. Mamunes P, Prince PE, Thornton NH, Hunt PA, Hitchcock ES: Intellectual deficits after transient tyrosinemia in the term neonate. Pediatrics 57:675, 1976
6. Menkes JH, Welcher DW, Levi HS, Dallas J, Gretsky NE: Relationship of elevated blood tyrosine to the ultimate intellectual performance of premature infants. Pediatrics 49:218, 1972
7. Rosett LH, Snyder P, Sander LW, Lee A, Cook P, Weiner L, Gould J: Effects of maternal drinking on neonate state regulation. Dev Med Child Neurol 21:464, 1979
8. Streissguth AP, Landesman-Dwyer S, Martin JC, Smith DW: Teratogenic effects of alcohol in human and laboratory animals. Science 209:353, 1980
9. Véghelyi P, Osztovics M, Kardos G, Leisztner L, Szaszovszky E, Igali S, Imrei J: The fetal alcohol syndrome: symptoms and pathogenesis. Acta paediatr Acad Sci Hung 19:171, 1978
10. Véghelyi PV, Osztovics M: The alcohol syndromes: The recombigenic effect of acetaldehyde. Experientia 34:195, 1978

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