The syndrome of atypical serumcholinesterase
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Chapter I deals with the aim of the investigation, which was to attempt to identify a clinical syndrome on the basis of which individuals with ASCE could be recognized in the heterozygous (or homozygous) form by means of easily distinguishable characteristics associated with the basic enzyme defect before the enzymic constitution of the blood was determined, in order to safeguard them from undesirable risks.

Chapter II contains a survey of the literature on suxamethonium apnoea, including a description of the pharmacological and neurophysiological aspects as well as the complications seen in normal and diseased persons.

Chapter III describes a pilot study concerning the detection of people with ASCE and the method used for the determination of serum cholinesterase in the blood, indicated by the dibucaine number (DN), the fluoride number (FN), and the activity in U/ml. Three groups are distinguished:

1. The normal homozygous type (NT): DN >71
2. The heterozygous, or intermediate type (IT): 50 - 71
3. The homozygous atypical type (AT): DN <35

Chapter IV concerns the genetic aspects of serum cholinesterase. The pedigree material has scientific relevance with respect to the enzyme polymorphism.

1. The mean DN and FN calculated for the NTs and ITs in the combined pedigree materials showed good agreement with the values found by other investigators in Caucasian populations. This also seems to hold for the ATs, but their number was too low to permit calculation of a reliable mean. The mean values obtained were DN(NT) = 79.50; DN(IT) = 61; FN(NT) = 57.7; and FN(IT) = 45.7. Since the sample could not be considered representative of the total population of The Netherlands, valid conclusions cannot be drawn concerning the incidence of these three phenotypes.

2. Investigation of relatives with the normal serum cholinesterase provided information about the variability of the FN values. In our material it could not be observed that a separate gene is responsible for low FN values.

2.2. Our results, too, show differences in serum cholinesterase activity dependent on sex and age, and it appeared that further variability of the serum cholinesterase activity is not due to alleles of the character ‘atypical’ but is genetically independent of them.

3.1. On the basis of the correlation of blood groups and serum factors with serum cholinesterase, it is shown that variations in serum cholinesterase activity in either direction are under genetic control. It was found that in families with high enzyme activity, the presence of the Rhesus factor E+ in the parents correlates with more children with an elevated serum cholinesterase activity than are found in absence of this factor. It seems possible that two types of elevated activity can be distinguished by their segregations, one genetically monofactorial and the other polyfactorial. With respect to the former type, E+ fathers proved to produce a relative excess of children with elevated SCE activity and E− fathers a relative shortage, irrespective of whether the genetic cause of the increased activity originated from the father or the mother.

3.2. With respect to the segregation of IT:NT in children of IT parents, the following was found. If the NT mating partner of an IT parent is E+, the IT:NT ratio in the children will be <1:1; if the NT parent is E−, the ratio will be >1:1; if the father contributes O to the child the ratio will be <1:1, and if it is non-O it will be >1:1. Combination of these two mechanism led to an intensification of the effect. It therefore seems probable that two selective mechanisms are operative in the transmission of atypical SCE to the offspring.

4.1. The possibility of an influence of the ABO blood groups on the DN was tested, and the following was found. In the presence of A1 antigen (or absence of H antigen) the DN of the [Ts is lower than in its absence. Since the ABH antigens occur on the cell membrane and since other findings appear to indicate that these antigens exert an influence on the permeability of the membrane, it seems possible that there is a relationship between this permeability and the level of the DN.

5.1. Close linkage between the Ch1 locus and the loci of blood and serum groups may be considered excluded.

5.2. With respect to the T-ratio (relation between sex, MN, and Rh), the following conclusions could be drawn: deviant T-ratios in children of MN mothers occur only in group O children, not in non-O children. A new finding is a deviant T-ratio in children with non-MN mothers.

Chapter V reports the morpho typological investigation.

Somatic characteristics of the intermediate type
(IT): A provisional inventory of the clinical aspects of the morphotype includes the following characteristics:
1. An underdeveloped musculature, i.e. 'thin' muscles.
2. A slender body build.
3. In dependence on the underdeveloped muscles, postural anomalies:
   a. kyphoscoliosis, originally correctable (age limit of correctability highly variable and dependent on occupation, etc.);
   b. moderate lordosis;
   c. 'sagging' abdomen;
   d. weak ligaments;
   e. splay feet, with hallux valgus and hammer toes, often at a very early age.
4. A low pulse rate (50-70b/min) shown electrocardiographically to arise from sinus bradycardia, but not the form seen in athletes.
5. Blood pressure in the range 110-120/70-80 mm Hg, even over the age of 40.
6. Disturbances of the peripheral circulation:
   a. acrocyanosis of the hands and feet, sometimes with numbness of fingers and toes,
   b. after prolonged standing, clearly visible veins on the legs.
7. Marked neuro-vegetative lability, expressed in dampness of hands and feet, readiness to sweat, flushing skin, positive dermography,
   a greater sensitivity to cold and extreme temperature changes than their NSCE relatives;
   a distinct 'respiratory' arrhythmia.
8. Prematurely grey hair.
9. Frail appearance and at first sight a 'sagging' expression.

The family data indicate that for mating type NT H x IT as compared with type NT x NT in which one (or both) parent(s) is/are S, the NT children are also too often of the S (i.e. slender) type (P <0.001). Furthermore, there proved to be an influence of the IT mother favouring S in the children (P <0.02).

Quantification of the somatic characteristics was done by the discriminant analysis and calculation of the probability score that a correct diagnosis has been made. The discriminant function score Y for a patient can be calculated with the equation:

\[ Y = -0.003X_1 - 0.023X_7 - 0.002X_{10} + 0.087X_{16} - 0.017X_{18} - 0.232X_{19} + 0.153X_{20} - 0.011X_{21} - 0.004X_{22} + 0.020X_{24} + 0.069X_{25}. \]

The probability p that a correct diagnosis has been made can be read from Table 43 (page 62). If the result for y is qualified by a plus sign, the probability P is greatest that the patient is an NT; if it is a minus sign, the probability is greatest that he is an IT. In the above equation the subscripts of x indicate the following items:
1: chronological age
7: distance from supra-sternal to umbilicus (or omphalon)
10: biacromial distance
16 & 18: measure of chest depth
19: measure of kyphosis
20: measure of lordosis
21-24: waist, hips, interiliacal distance, interspinal distance, respectively
25: length of the hand

This approach provides the clinician with an objective method for the evaluation of his patient and can replace Sheldon's method, to which various disadvantages are attached. Besides the addition of new information by the introduction of new independent measures into the discriminant function, the method offers several other possibilities for extension, the most important being a means to arrive at a differential diagnosis.

Chapter VI concerns the physiological investigation. As can be judged from points 4-7, the circulatory anomalies in individuals with ASCE are very distinct, and it would therefore be desirable to find a way to evaluate them objectively.

In a pilot study of eighteen paired ITs and NTs between 20 and 35 years of age, the ECG, respirogram, and plethysmogram of the fingers were investigated. The cardiac arrhythmia was quantified by a computer analysis of the R-R intervals. There is a distinct difference between NTs and ITs, as can be seen from the results. The slow pulse rate observed clinically in the ITs can be explained from the long R-R intervals. The distribution of these long intervals is irregular. The respiration contributes to this irregularity but is not the only causal factor involved here, and further research is required to elucidate this point.

The disturbances of the peripheral circulation could also be quantified. The reaction of the capillary bed differs widely between IT and NT relatives.

The unpleasant sensation of pain experienced by the IT on exposure to low temperatures was observed in the test situation, and the anamnestic data on this point could therefore be considered reliable. On the basis of the reactions of the ITs to the different test situations, they may be considered to have a labile circulatory system with an inadequate capacity to
adjust to extreme temperature changes. This phenomenon must also be taken into account for practical purposes. The sensation of pain experienced by ITs on exposure to cold requires further investigation.

Chapter VII concerns the psychological characteristics of individuals with the atypical serumcholinesterase and their families, as compared with relatives with the normal enzyme.

The Adult with ASCE.

1. General impression: On first acquaintance the impression is that of a friendly, initially somewhat shy, inhibited, reserved, and cooperative person, who tends to have a wait-and-see attitude. The facial expression is somewhat tight and tense. When they feel they can trust one, the coolness disappears and the facial expression becomes highly mobile and expressive, with an open, honest, and very sensitive expression, giving an effect of frailty.

2. Special character features.
They are excessively alert. They orient themselves rapidly, are highly aware of the people and things around them, whose true value they can estimate with extra ordinary rapidity. Their reticence prevents others from noticing how well they can evaluate them and the situation. Other people are often mistaken in their evaluation of ASCE individuals, who are helpful, friendly, and gentle and are never the first to become aggressive in certain situations that might otherwise be provocative. Behind the expression of coolness and immobility an enormous sensitivity is hidden. Their emotional life is warm and deep, with prolonged after-effects. Their social engagement is great. They never seek the limelight. They are people who conceal their emotionality at any cost, but they also persist in converting this inner engagement into practical action. In this they can be extremely tenacious. They are highly reliable, honest, hard workers. These individuals are not suited for mass production or assembly lines. They attempt to find individual work, requiring creativity, precision, and speed. They are soloists, with a high degree of social engagement, making heavy demands on themselves and their surroundings.

3. Comparison of the character features of individuals with the atypical and normal enzyme in the same family. The individuals with the normal type have a greater capacity for distatination from their work and their surroundings. They do not hesitate to strike back when they are attacked. They are harder and less cautious than the ITs and may be considered more egotistical.

The child with the atypical serumcholinesterase.

This child seems frail. He is quiet and industrious. He never tries to be a ringleader. He usually has one good friend, carefully chosen. These children do not shine in physical activities. They do not perform well. Their stamina remains below the level of the NT children in the family. They are not children who arouse aggression in others. For this, a comparison can be made with children having muscular dystrophy.

The psycho-physiological investigation showed the same reaction of the vascular system during mental stress as the effect seen during physical stress.

The final conclusion is that individuals with atypical serumcholinesterase may have not only a typical physical build but also a typical character structure. They show many points of correspondence with the sensitive character structure described by Kretschmer, but differ from this type in the following ways: they are less ambitious; although they proceed quietly, they can reach very high working tempos. Because they can size up a situation so quickly, they can take any necessary steps with little delay. Their inhibitions disappear when the necessity for speed is evident.

Decompensation and clinical phenomena in adult ITs and ATs

Before a clear clinical picture evolves in these individuals, there is usually a prolonged transitional phase between health and sickness. This is a kind of alarm phase, characterized by a sense of discomfort and powerlessness, uncertainty, and restlessness. This is followed by symptoms of masked depression. In the phase of real clinical symptoms the neuro-vegetative dystonia predominates. The high degree of tension and the lack of physical relaxation, predispose these people to myocardial infarction and gastrointestinal and gall-bladder complaints, in other words their problems lie in the field of psychosomatic medicine.

The pattern underlying both the physical and psychological reactions can probably be brought under the same common denominator and would be explained by inadequate function due to ASCE. It has been possible to identify a clinical syndrome associated with the basic enzyme defect.

Recommendations for the prevention of decompensation in individuals with atypical serumcholinesterase lie in the field of physiotherapy and interpersonal approach.