Idiopathic Dystonia Musculorum Deformans

I. The Hereditary Pattern

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INTRODUCTION

IT IS GENERALLY AGREED that dystonia musculorum deformans may be associated with a number of well delineated pathological entities, such as Wilson's disease, various of the encephalitides, vascular malformations, idiopathic calcification of cerebral vessels, and others (Hallervorden, 1957). In contradistinction to those "symptomatic" forms of dystonia this paper is concerned with the idiopathic form to which the term dystonia musculorum deformans should be confined according to Herz (1944).

Dystonia is conventionally classified as an extrapyramidal disease. The ratio between affected males and females is about 60:40. No explanation for this sex distribution has been offered, as yet. The disease usually begins during childhood or adolescence.

The chief symptoms are dystonic posture and dystonic movements. The latter are true hyperkinesias and are characterized by relatively slow, long sustained, powerful, nonpatterned, contorting activities of the axial and appendicular muscles. The muscles most commonly involved are those of the neck, trunk, and proximal portions of extremities. Involvement of unilateral muscle groups often results in bizarre torsion movements, hence the alternative term "torsiondystonia" for the disease. Volitional acts are often seriously compromised. The dystonic movements disappear during sleep and under general anesthesia. "Dystonic posture" is the term used if the end position of a dystonic movement is maintained for any length of time. Eventually this may lead to contracture deformities. Various dystonic postures are exemplified by Fig. 1.

The onset is gradual, with drawing sensations in axial and appendicular muscles. Gait is usually impaired first, but writer's cramp or torticollis may also constitute the initial symptom. Muscle hypertrophy may result from continuous activity, eventually leading to such deformities as kyphoscoliosis, pes equinovarus and others. Speech is often impaired. Sensation and mentation are rarely affected. Laboratory findings are within normal limits. The course varies, ranging from complete incapacitation to a mild nonprogressive illness. Sometimes remissions may occur.

The earlier reports on the disease noted Jews to be exclusively affected. Subsequent studies, however, invalidated this notion.

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FIG. 1. Family P (see Fig. 2) Standing from left to right: IV-10. Note the dystonic posture of head, trunk and legs which has resulted in a moderate kyphoscoliosis and inversion of the feet V-10. Appears normal on this picture. V-14. Appears normal on this picture. V-11. Note spastic torticollis and dystonic posture of left arm. Sitting, V-13. Severe kyphoscoliosis and torticollis. Dystonic posture of left hand. Acquired bilateral pes equino-varus.

Schwalbe (1908) who reported the disease in three siblings is usually credited with the discovery of the condition, although Gowers had described the disease in two brothers as early as 1893. Despite this familial occurrence, Mendel (1919) in the first monograph on the subject mentioned that the condition was obviously not inherited. This somewhat surprising conclusion probably stemmed from the authoritative statement of Oppenheim (1911) who reported four instances of the disease, all of which were sporadic. He also mentioned the cases of two siblings who exhibited a clinical picture somewhat similar to the other cases. However, Oppenheim was not certain as to the diagnosis in those cases. In his textbook, Oppenheim (1923) stated that nothing definite was known regarding the heredity of the condition, although siblings had been affected in two instances. A similar view was expressed by Herz (1944) in his classic study of the disease.

On the other hand, Polish and Russian authors consistently proposed dystonia as a definitely inherited disease. Mankowsky and Czerny (1929) reported on two families, the first with a seemingly recessive, the second with a dominant pattern of inheritance. Regensburg (1930) described four families, among them the original observation of Schwalbe (1908), in which the disease occurred in the form of a Mendelian dominant.

Beilin (1934) examined 41 members of a family of 104 in which the disease was recessively inherited.

The purpose of this communication is to present evidence that idiopathic dystonia is definitely inherited and is transmitted predominantly as a Mendelian dominant. The second contention is suggested by the inheritance pattern of a family reported here for the first time, and is in line with most of the previously known instances of familial occurrence of the disease.

FAMILY HISTORY

The family history was obtained as fully as possible, although a certain lack of cooperation was encountered among some of the members. The chief problem was a reluctance to admit to a familial disabling disorder.

The family is of English extraction and, as far as could be ascertained, has lived in rural Ohio for at least six generations. Consanguinity was not found during this period of time. An effort was made to examine each descendant of the first person known to have been affected by the disease (III-16 in Fig. 2). Furthermore, the siblings of those individuals and their descendants who came from unaffected families, but had produced diseased children (III-3 through 9, IV-1 through 9 and VI through 8 in Fig. 2), were questioned and examined whenever possible.

It is felt that the information set forth in the family tree (Fig. 2) is generally accurate. In those instances in which the individual could not be examined the information was corroborated by at least two independent informants. This is invariably true for that part of the family in which the disease is inherited in a direct line.

EXPLANATION OF THE PEDIGREE

General Information. A cross indicates that the individual was deceased at the time of the investigation. The age indicates either the age at the time of death or the age in 1958, the time of investigation. The heavy lines indicate the connections between the various generations through which the disease has been passed down.

Specific Information

I 1 died of old age; 2, 3, and 4 no information available.

II 1 died of old age; 2 no information available; 3 and 4 died of old age.

III 1 died of old age; 2 died of heart failure; 3 through 7 and 9 were healthy individuals. Information regarding this family was obtained from the children of 5 and 7 who stated that there is no nervous or mental disorder known in the offspring of these six persons, who number more than 100 at the present time. Eight has been described by members of his family as a healthy, normal individual; by members of his wife's family as a periodic drunkard who would spend all his money on liquor and then would work for a number of weeks. He was a very poor provider. All his children were either brought up in foster homes or in the County Children's Home.

Ten died as an infant; 11 died at age 9 from an accident. Twelve through 15 and 17 through 20 were eight siblings having descendants numbering more than 100, none of whom is or has been affected by dystonia or by any other

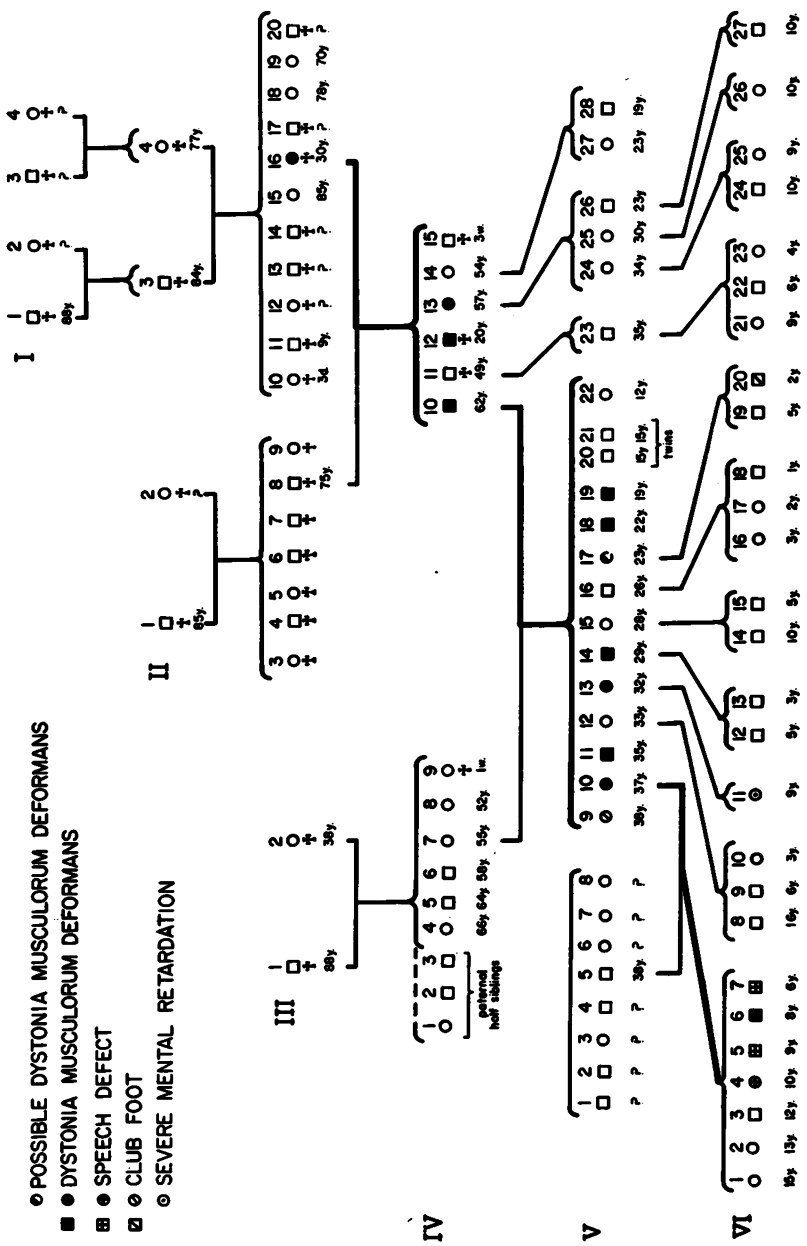

FIG. 2. Family P. See text for explanation.

nervous or mental disease. This information was obtained from 18 and from the widow of 20 and was corroborated by several of their descendants. Sixteen is the first known case of dystonia in this family. The patient showed the first signs of the disease during childhood, allegedly about age 10, and was totally disabled at 23. She died at 30, reportedly from pneumonia.

IV 1 through 6 and 8 have had 10 children, 19 grandchildren and one great-grandchild. All these individuals are normal. There are no signs of nervous disease in this family. This information was obtained from 4 and 5. Nine died as an infant.

Ten has been mildly afflicted with dystonia since age 21 (Fig. 1). The condition has been stationary since. Eleven has never been sick and was killed when his airplane crashed. Twelve had severe dystonia from age 5 on and died, completely crippled, in the County Children's Home at age 20. This child is described as having been similarly affected by the disease as was his mother, III-16. Thirteen showed the first signs of the disease after the delivery of her third child at age 25. Dystonic symptoms have since been stationary after a progressive course of approximately one year. Fourteen could not be examined. According to her own statement, corroborated by an aunt, she has never shown any signs of the disease. Fifteen died at age 3 weeks.

V 1 through 8 are healthy and are not afflicted by nervous or mental disorders, according to statements by 5 and 6 who have been examined.

Nine has a clubfoot, surgically corrected, but no other defects. Dystonia developed in 10 (Fig. 1) after the birth of her seventh child at age 31 and has been practically stationary since. Eleven (Fig. 1) showed first signs of dystonia at age 17 at which time St. Vitus dance was diagnosed. He is able to work, however. Twelve has not been examined and is allegedly healthy. Severe dystonia began in 13 (Fig. 1) at age 11 and she is now completely crippled. Fourteen (Fig. 1) has mild dystonia in the form of temporary limping, blepharospasm, and mild torticollis. Fifteen and 16 have not been examined; they are allegedly healthy. Seventeen developed a temporary limp at age 10, which has now subsided. This person is in poor general health at present. She has not been examined, but probably has dystonia. Classic dystonia began in 18 at age 9, and since age 13 he has been completely crippled. Severe dystonia began at age 5 in 19, who is now completely crippled. Twenty and 21, identical twins, are both healthy. Twenty-two through 27 have not been examined and are allegedly healthy. Twenty-eight has not been examined. According to information obtained from the attending psychiatrist, this boy is severely neurotic and retarded. There are, however, no signs of dystonia.

VI 1 through 3 are bright and intelligent children. Four, 5, and 7 have speech difficulties, cannot pronounce "f" and "s" and are mentally retarded to the extent that they entered public school with a delay of two years. Six has overt dystonia, developed at age 5. He is not crippled, but has a typical dystonic gait. Eight through 10 are allegedly healthy. Eleven has severe mental retardation and is now attending the first grade. This child shows several stigmata in the form of abnormal position of teeth and pronounced prognathy,

but has no signs of dystonia. Twelve through 19 are allegedly healthy. Twenty has bilateral congenital metatarsi vari. Twenty-one through 27 are allegedly healthy.

ANALYSIS OF PEDIGREE

It is evident from the pedigree that there is marked evidence for the inheritance of dystonia musculorum deformans, the disease having been transmitted through at least four successive generations. It is very probable that some members of the last generation born to an affected parent and recorded here as free of the disease will ultimately develop it, for the experience of this family shows that the onset in some instances has been delayed to as late as the age of 31. On the other hand, it has never appeared earlier than the age of five.

Beginning with the first instance of the disease in III-16, three of her six children developed dystonia. Of the 14 children of IV-10, six or possibly seven have the disease. Apparently 50 per cent of the offspring of two successive generations are affected. This, of course, suggests a Mendelian dominant which, at least in these generations, shows complete penetrance. That the three children of IV-13 and her four grandchildren have been free of the disease does not refute such a mechanism of inheritance.

Within this family there is a considerable variability of expressivity of the disease. For instance, V-14 shows symptoms of dystonia in a very mild form, manifested by temporary limping, torticollis and blepharospasm. At times this patient appears almost normal. On the other hand, three of his siblings are totally crippled and helpless. V-10 has neither spontaneous movements nor the typical dystonic posture. Yet, upon performing certain volitional movements, typical dystonic features can be easily elicited. Certainly in cases like these two, one could take the position that such manifestations do not justify the diagnosis of dystonia. Yet, it would be illogical to consider any other diagnosis in view of the fact that grandmother, father, siblings, and one child are so definitely affected by dystonia. Applying "Occam's razor" of scientific parsimony, it is certainly the most logical conclusion that this family exhibits "formes frustes" as well as full-fledged cases of dystonia. Obviously, the strict diagnostic criteria as put forth by Herz (1944) were not applied to the subject cases. Whether the congenital abnormalities of the feet encountered in cases V-9 and VI-20 are related to dystonia is a matter of speculation. The question will be discussed in more detail in a subsequent paper dealing with the clinical features of dystonia as observed in this family.

In conclusion, it seems safe to assume that in this family the disease is propagated by a Mendelian dominant gene, with varying expressivity, but probably with complete penetrance. The fact that the first affected of this family was a sister of eight healthy siblings, all of whom have healthy offspring, is difficult to explain. Since this patient was the seventh child of eleven, there is little probability of illegitimacy, so that a spontaneous mutation may be considered as the probable explanation.

REVIEW OF LITERATURE

There are at least 29 instances of familial occurrence of dystonia reported in the literature. In twelve of these the disease occurred only in members of one generation

(Abrahamson 1920, Bernstein 1912, Gowers 1893, Jakob 1924, Kehrer 1936, Oppenheim 1911, Price 1921, Santangelo 1934, Spiller 1913, Svejcar 1924, Taylor 1920, van Bogaert 1946). Kehrer (1936) suggested that his cases (three sisters) were the result of an exogenous factor in the form of a maternal disease with bouts of exacerbation during the pregnancies. Herz (1944) considered the observations of Gowers (1893) and Price (1921) as not proven instances of the disease. Oppenheim (1911) also was not certain as to the diagnosis in his cases, and finally van Bogaert (1946) considered the two brothers he examined to be instances of choreoathetosis with torsion spasms. Hallervorden (1957), however, included the latter cases in his hiscussion of dystonia.

This leaves seventeen families in which dystonia was observed in members of different generations. Again, Herz (1946) excluded a number of these, either on the basis of insufficient data or because he felt they belonged to other well defined morbid entities. The former exclusion applies to the family reported by Dawidenkow and Solotowa (1921) in which the father, his sister and one daughter suffered from what the authors considered was dystonia. In the case of Fossey (1922), to be discussed in detail later, Herz (1944) felt that there was sufficient evidence to suspect Huntington's chorea. The cases of Benedek and Rakowitz (1940) were complicated by congenital deformities of the face and might well constitute a different clinical syndrome. The clinical data in the cases of Munch-Petersen (1930) leave some doubt as to a diagnosis of dystonia.

The remaining thirteen families will be discussed in detail. Nine of them conform to the stipulations for a dominant inheritance pattern, (Beder 1926, Dzerschinsky 1925, Jankowska 1934, v. Keyserlingk 1956, Mankowsky and Czerny 1929, Regensburg 1930 (three families), van Bogaert 1940-41). Four are suggestive of a recessive mode of inheritance (Beilin 1934, Mankowsky and Czerny 1929, Santangelo 1934, Wechsler and Brock 1922).

DOMINANT CASES

By far the most convincing example of a dominant pattern of inheritance is the Lewin family (Fig. 3) independently described by Schwalbe (1908), Regensburg (1930), Jankowska (1934), Rose (1937), and Vogt (1942). This pedigree also exemplifies the pitfalls of research.

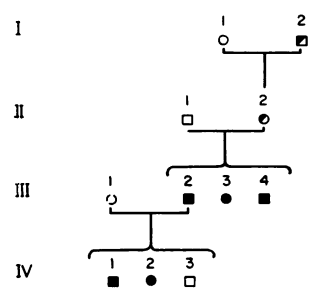

FIG. 3. Family Lewin after Schwalbe (1908), Regensburg (1930), Jankowska (1934), Rose (1937), Vogt (1942), and Hallervorden (1957). See text for explanation.

No information is available on I-1. I-2 suffered from tremor of the hands after having been buried alive in the Turco-Russian War. His son-in-law, II-1, was allegedly healthy but his daughter, II-2, also had shaking of hands and feet during her later years of life. III-2, 3, and 4 are the three siblings first described by Schwalbe (1908). III-3 died after an illness of sixteen years duration. Her brain was examined by C. and O. Vogt (1937), who found an atrophy of the small striatum cells, of the nucleus centralis thalami and of the astrocytes throughout the brain, with overgrowth of oligodendrocytes. III-4 committed suicide after six years of illness. III-2 was the least affected of the siblings. He showed his first symptoms at age 15, but his condition remained stationary thereafter. At age 33 he married a healthy girl, III-1, from a healthy family who bore him three children. The first son, IV-1, developed dystonia at age 6 and died 15 months later. His brain was examined by Rose (1937) who found lessions similar to but less pronounced than those described by the Vogts (1942). IV-2 became ill at age 2 and was still alive at age 9. IV-3 was healthy at age 7.

This family is a lucid example of how a critical and detailed genealogic study can reverse previous interpretations. Regensburg (1930) had already pointed out that Schwalbe (1908) had not paid any attention to the familial trend of shaking of the extremities, presumably because he could not understand Russian, which was the native tongue of these patients. Partly on the basis of this omission the hereditary character of the disease was seriously questioned by its most diligent students. Another important factor brought to light by this pedigree is the variable expressivity. III-2 was only mildly affected by the condition. The disease remained stationary for decades. This patient never developed speech disturbances. The dystonic cramps were painless. His two affected children, as well as his two siblings, ran an entirely different course and exhibited far more severe symptoms. In both children the disease was rapidly progressive, leading to an early crippling. Both suffered from painful spastic contractures, and IV-1 lost his speech completely. In this respect there is much similarity between these cases and IV-10 and his children, V-13, 18, and 19 of our reported pedigree.

On the basis of the anatomical findings and the apparent dominant pattern of inheritance, Hallervorden (1957) is inclined to consider this form of dystonia as a variant of Huntington's chorea. In support of this assumption, he quotes the family described by Fossey (1922) (Fig. 4). Unfortunately, this paper is fragmentary and the author's contentions are poorly documented. Most of the pertinent statements are quotations of W. G. Spiller's opinions, who apparently did not care to publish his observations. There is, however, a possibility that Fossey's cases might include those which were described by Spiller (1913).

After having become familiar with Oppenheim's original work, Spiller felt compelled to change the diagnosis of three siblings, all inmates of the Philadelphia General Hospital, from Huntington's chorea to dystonia. He pointed out that the importance of his observation rested upon the familial occurrence and the fact that the patients were not Jewish. (It will be recalled that in those days dystonia was believed to occur almost exclusively in Jews and not to be an inherited disease.) The members of the family reported by Fossey, were also inmates of the same

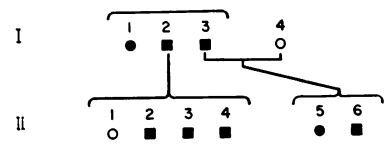

FIG. 4. Family of Fossey (1922). See text for explanation.

hospital. Furthermore, Spiller had diagnosed cases II-5 and 6 as instances of dystonia. The hospital records gave the diagnosis of Huntington's chorea for I-2 and 3, and II-2 and 3. I-1 was diagnosed as having suffered from nervous trouble.

The only point in favor of chorea in Fossey's case II-5 is the fact that the proband became sick at age 33. For the other family members, the age of onset is not given. While an age of onset of 33 does not rule out dystonia, it is nonetheless not the rule. Mankowsky and Czerny (1929) report on the father of two children with dystonia, who showed the first signs of the disease at age 32. On the other hand, when Hallervorden (1957) contends that the dystonia occurring in the Lewin family is a variant of Huntington's chorea, he ignores completely the fact that the latter disease begins between the ages of 21 and 60 in 94 per cent of all cases. Furthermore, hereditary chorea is extremely rare, if not nonexistent, among Jews.

The family on which Mankowsky and Czerny (1929) based their case for a dominant pattern of inheritance is shown in Fig. 5. II-2 became sick with choreatic and dystonic movements after he had lost his fortune at age 32. III-1 and 1 were twins. III-2 died as an infant and III-5 at age 7.

Here the solitary appearance of one diseased member in a sibship of six again suggests a spontaneous mutation, as stipulated for our III-16. III-1 and III-6 had classic dystonia. III-3 apparently had a *forme fruste*. These authors quote the observations of Beder (1926), a father and daughter with dystonia, and of Dzerschinsky, with father and son affected by the disease, as supportive evidence of dominant inheritance.

In addition to the famous Lewin family, Regensburg (1930) published three more instances of familial occurrence. The most striking is the family Frdk (Fig. 6). I-1 came from a healthy family. I-2 and 3 and II-3, 4, 5 all showed classic dystonia. III-1 and 2 in addition to dystonia exhibited signs of muscular dystrophia. II-1, 2, 6, 7, 8 had speech difficulties but otherwise no signs of the disease.

In the family Nsls, the father and two children were affected and in the family L. B., the father and four of his six children had dystonia.

Haenisch (1914) observed dystonia in father and son.

Van Bogaert (1940–41) reported on a mother and her two daughters who were affected by spastic torticollis. Several members of the family exhibited tremor and dystonic movements of varying degrees.

Von Keyserlingk (1956) described a father and four of his five children affected by dystonia. While two of the children were severely diseased, the father's symptoms were scant and practically restricted to speech difficulties. His sister was similarly affected; no information was available on seven other siblings. Von Keyserlingk

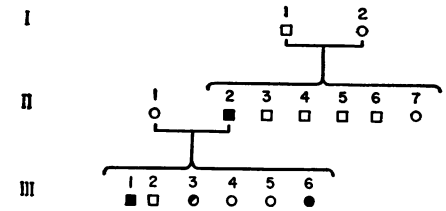

FIG. 5. Family II of Mankowsky and Czerny (1929). See text for explanation.

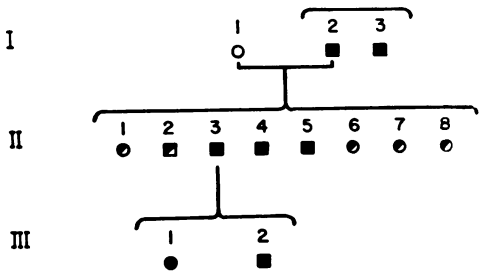

FIG. 6. Family Frdk of Regensburg (1930). See text for explanation

points out that the speech difficulties are *formes frustes* or abortive forms of the condition.

RECESSIVE CASES

The first observation was reported by Wechsler and Brock (1922). In their case #3 a remarkable familial tendency was discovered (Fig. 7). Unfortunately, the authors did not elaborate on the pedigree which they published. It was stated only that the grandparents in generation I were in good health. Because of the paucity of pertinent information on II-2 and 3 it is tempting to speculate on the possibility that these cases had a *forme fruste* of dystonia or that there was incomplete penetrance. In any event, the occurrence of the disease in the offspring of two supposedly unaffected siblings would require that each had married a heterozygote. However, the rarity of the disease, and the absence of consanguinity in the pedigree would suggest that the above explanations are preferable to that of the disease being a recessive in this family.

A somewhat similar situation exists in regard to the case of Mankowsky and Czerny (1929), on which they elaborated the hypothesis of a recessive inheritance (Fig. 8). I-2 was allegedly healthy. I-3 and 4 suffered from what was diagnosed as Huntington's chorea. II-2 died as an infant. II-3 and 4 were affected by dystonia. The same criticism we have made pertaining to the case of Wechsler and Brock applies to this observation.

The most diligently elaborated pedigree of a family with dystonia was published by Beilin (1934–35). It is too complex and large to be included here. Beilin found five cases of severe and four of mild dystonia among 104 members of one family

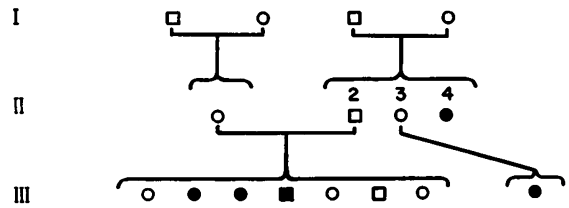

FIG. 7. Family of Wechsler and Brock (1922). See text for explanation.

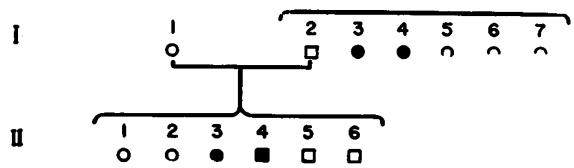

FIG. 8. Family I of Mankowsky and Czerny (1929). See text for explanation.

spanning six generations. The author applied rigid standards for the clinical diagnosis and did not speculate on the possibility of *formes frustes*. This is exemplified by his case D-10, the mother of two children with mild dystonia. This person suffered a contracture of one arm due to painful muscle cramps during adolescence which were never clarified etiologically. Yet she is listed as healthy and unaffected. There is one branch of this family in which consanguinity occurred. Unfortunately, all four children born to this couple died in infancy and childhood from epilepsy, but none showed any signs of dystonia. Another shortcoming of the chart of Beilin is the fact that some 30 members of the 5th and 6th generation of the family had emigrated to the United States, so that no information could be obtained first-hand. It is interesting to speculate on the possibility of some of these members having shown up in American medical journals as instances of dystonia. Finally, the author encountered considerable difficulties in obtaining information. The family members tried to dispel any suspicion of a familial disorder, pointing to impossible and ridiculous factors which were said to have precipitated the outbreak of the disease in the affected members. Therefore, it must be concluded that Beilin's family chart, although investigated with zeal and intelligence, is not necessarily proof of a recessive pattern of inheritance of dystonia.

The strongest case for such a contention was presented by Santangelo (1934). In this family three of five children born to apparently healthy parents were affected by the disease. The important fact is that the father's father and mother's father were first cousins. Nothing, however, is mentioned about ancestral and collateral generations.

It must be admitted that consanguinity increases the chances of both parents being carriers of a recessive gene, especially where a condition as rare as dystonia is concerned. Yet, considering the fact that marriages as close as second cousins are common in Italy, this case is only slightly indicative of recessive inheritance.

DISCUSSION

In evaluating the information from the literature and from the present report, one cannot escape the conclusion that there is much evidence in favor of a Mendelian dominant in the propagation of the disease. In fact, were it not for the observations of Santangelo (1934) and Beilin (1934–35), one would certainly be inclined to disregard whatever evidence had been presented in support of a Mendelian recessive. Even in the cases assumed to be recessive, but certainly in all those claimed to be dominant, the expected ratio of 50:50 of affected and nonaffected is met, with the notable exception of Beilin's family (1934–35).

As the situation stands now, it is probably safe to assume that in most instances a Mendelian dominant seems to be the mode of inheritance. But it is worthwhile to recall the statement of Kehrer (1936) that pure dominant and pure recessive inheritance are only the extremes of all possible modes of inheritance. Also, it should be remembered that several ailments are known in both dominant and recessive forms.

The study of the subject family and the review of the literature of the hereditary aspects of dystonia permit us to draw a number of other conclusions.

Clinical and Morbid Entity. The massed occurrence of dystonia in several families can be safely considered as evidence for a specific clinical entity. Whether dystonia is a morbid entity of course depends upon the pathomorphology of the condition. This could be investigated so far in only two instances of the Lewin family. The similarity of the histopathology in these two cases allows one to postulate a morbid entity at least for this family. Since Quandt (1956) and others were able to demonstrate identical findings in single, i.e. sporadic, cases of idiopathic dystonia, there is reason to assume that dystonia musculorum deformans actually represents a morbid entity.

On the other hand, it should not be ignored that van Bogaert (1946) examined two brothers with torsiondystonia and choreo-athetosis in which the lesions of the CNS were restricted to pallidum and corpus of Luys and, therefore, were entirely different from those described by the Vogts (1942), Rose (1937), and Quandt (1956). Furthermore, the various types and sites of pathologic lesions in cases of symptomatic dystonia provide ample evidence that the clinical syndrome can be produced by a number of differently located lesions and their combinations.

Thus, it appears safest to leave the question of the specificity of morbid entity unanswered at this time.

Further Classification. Herz (1944) proposed that dystonia could be further classified into an early form occurring shortly after birth, the juvenile form with the onset between 5 and 15, and the late form after 15 years of age. Experience with the hereditary cases of the disease shows that such classification is somewhat arbitrary, because in one and the same generation the disease might begin any time from birth to age 33 or even later. This situation which also prevails in other heredo-degenerations brings to mind the remark by van Bogaert (1948) that the heredo-familial diseases, whether congenital, precocious, or of late manifestation, are but the expression of one and the same genetic disorder. It depends on the degree and the moment

of intervention of one or a number of perturbing factors when the genotypical disturbances become phenotypically manifest. These perturbing factors are either other coexistent but autonomous predispositions (genotypical milieu, apparently dormant or "*restant*" genes), or are exogenous or "*peristatic*" causes.

Nonetheless, Herz's classification is not without merit, simply because it facilitates the prognosis of the further development of the condition. As demonstrated by the familial cases collected here, the disease usually runs a more severe course the earlier it becomes manifest. Conversely, the later the onset, the greater the chance for arrest or remission. This, however, is true only as a generality.

Clinical Forms of Dystonia. The marked variations in expressivity noted by practically all the investigators of affected families, calls for a revision of the hitherto accepted diagnostic criteria. Since the clinical manifestations of the afflicted members of the subject family will be treated in a separate communication, only a few pertinent points will be made here.

Herz (1944) gave the following criteria for the clinical diagnosis:

a) Selective systemic symptoms in the form of dystonic movements and postures.

b) Gradual development, without recognizable etiological factors at the onset.

Obviously, these rigid diagnostic criteria would not permit making a diagnosis in some cases in which there is evidence that the person had received as well as propagated the gene responsible for the disease. This is, for instance, true of our case V-10 who has no dystonic postures and exhibits dystonic movements only under certain restricted conditions of volitional movements. In other words, all *formes frustes* would be excluded if Herz's diagnostic criteria were accepted without reservation. However, it is exactly the *forme fruste* which is of the greatest importance, should attempts be made to eradicate the condition by eugenic counseling.

Secondly, the stipulation that the disease develops without recognizable etiologic factors could be misleading. Certainly, the etiology of the condition seems to be a heredo-degenerative process, but it must be kept in mind that the onset of the clinical manifestations can be "triggered" by any number of exogenous "*peristatic*" factors. This is illustrated by one of the patients of Mankowsky and Czerny (1929) and might also explain the cases of Kehrer (1936) and others.

It is, therefore, proposed to set more flexible standards as to the diagnostic criteria and to incorporate an evaluation of possible genetic as well as "*peristatic*" factors into the differential diagnostic considerations.

Sporadic Cases. It should not be ignored that the number of sporadic cases of dystonia by far exceeds the familial cases. This fact has certainly played an important role in obscuring the hereditary nature of the disease and seems, at least superficially, to argue against a dominant inheritance. It will be noted that in Huntington's chorea, the prime example of a dominantly inherited neurologic disease, the ratio is reversed. This apparent discrepancy can be resolved by the following arguments:

In the first place, it is important to remember that dystonia, unlike Huntington's chorea, is primarily a disease of childhood. While it does not necessarily shorten the life span, its crippling and disabling effects certainly eliminate many patients from propagation, because these events usually occur before or at puberty. Indeed, most of the so-called sporadic cases reported in the literature had no family of their own.

The fact that other members of the sibships remained unaffected could then be explained on the basis of a mutation.

Secondly, it can be safely assumed that most of the *formes frustes* go unnoticed so that the carrier parent is usually considered to be normal. Thus, the high incidence of sporadic cases and the relative scarceness of familial instances of idiopathic dystonia neither disprove the hereditary nature of the disease nor do they argue against a prevailing tendency of dominant inheritance.

SUMMARY

Genetic studies have been made on a family in which twelve individuals are affected with idiopathic dystonia musculorum deformans. This condition has been traced through four generations and is inherited as a Mendelian dominant trait with complete penetrance, but with very variable expressivity.

A review of 29 instances of familial occurrence of the condition, reported in the literature, reveals that the disease is most frequently transmitted by a dominant gene, although a recessive mode of inheritance may exist.

The importance of having presented new evidence of dystonia musculorum deformans being a heredo-degenerative disease and for its prevention by genetic counseling rests primarily upon the possibility of better delineating and understanding the "*formes frustes*" of this disease. The different clinical manifestations of these abortive forms of dystonia will be described in a separate publication.

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