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Myasthenia gravis in childhood and adolescence. Report on 209 patients and review of the literature

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Authors review the different theoretical and practical problems of childhood and adolescent myastenia gravis, including the heterogeneous group of congenital myasthenia and the big casuistics of the literature. There are reports on 113 cases with childhood myasthenia gravis and 96 cases of adolescent myasthenia. Ratio of these forms ranged 10.76% in childhood myasthenia and 9.14% in adolescent age, resp., 19.9% of the whole patient material. A classification is given concerning juvenile myasthenia: 1. Neonatal (transitory) myasthenia. — 2. Congenital (local, non-progressive) form. — 3. Congenital form with late generalized symptoms. — 4. Myasthenia simulating brain-stem process. — 5. Generalized childhood myasthenia. — 6. Adolescent type myasthenia (juvenile form). — 7. Associated myasthenia, myasthenic syndrome or reaction. A new form of the disease is described in which the congenital myasthenia changes into generalized form in the later course of the disease. Report is given on thymectomies in childhood and adolescence which produce in general excellent results. Thymic pathology and activity are dealt with.

Myasthenia gravis (MG) was given special interest since its original description by Sir Thomas Willis just 300 years ago. The first time at the turn of this century upon the correct analysis of the clinical symptoms and recognition of the thymus — MG relationship. Then in the 1930s upon discovery of the chemical nature of neuro-muscular block, (the pathological basis of the disease), furthermore, upon introduction of successful drug therapy and thymectomy, as treatment method. Finally in the 1960s when the autoimmune nature of the syndrome was proved. Childhood MG has remained a neglected question in the literature [34] in spite of the increased number of related studies. In the early period, a few articles were published [3, 36, 68, 85, 118], furthermore familial, congenital MG [56] and myasthenic respiratory crisis [57] became known. Transitory MG in a newborn infant of a myasthenic mother was first described by Strickroot et al [93]; this transient form of MG is called neonatal in modern literature.

The big childhood MG casuistics, figuring in later literature are shown in a table (Table I). The upper age limit,

TABLE I

Large casuistics of the literature

Authors	No. of patients	Mean age of onset	Ocular form %	Gener. form %	Surgery %	Result %
Millichap, Dodge [61]	35	12y	17	80	60	86
Tether [112]	89	—	—	—	—	—
Hokkanen [48]	25	—	—	—	—	—
Fukuyama et al [35]	76	4.6y	44	50	—	—
Osserman, Genkins [74]	131	9y	—	—	—	—
Schugk et al [87]	36	—	—	—	—	—
Ryniewicz, Badurska [86]	47	7.5y	—	—	60	68
Snead et al [92]	32	7.7y	37	63	22	29
Seybold et al [88, 89]	102	10.4y	—	—	47	38
Oosterhuis [71, 72]	112	—	30	—	—	—
Rodriguez et al [84]	149	13y	—	86	57	79
Hawkins et al [45]	27	4.5y	24	3	—	—
Roach et al [81]	11	3y	55	45	—	—
Szobor [96, 104],	113	9.9y	34	60	35	92+
Szobor et al. present study	96	16.1y	5	90	75	80++

+ Patients in childhood
++ Patients in adolescence

however, is uncertain in some statistics [84, 87, 92, 112], so the true number of childhood cases cannot be established in some of these references. The first bigger casuistic and successful thymectomies in childhood MG were described by Millichap and Dodge [61]. The first congenital MG in a newborn whose mother was not myasthenic was observed by Bowman [9], then this form in siblings, too, by Levin [56]. He stressed the primary or exclusive alteration of the extraocular muscles in this form. Congenital MG became gradually an independent disorder. This form could namely be separated from acquired adult MG both clinically and immunologically: Congenital MG is, in general, local (ocular), non-progressive in its nature, and no ACh-receptor antibodies can be found in the serum of the patients. The literature of this MG form was especially enriched by the activity of Engel, Engel et al [23, 24, 25, 26, 27, 28, 29, 30] Hart el al [44], Vincent et al [113]. Congenital MG can be considered to be a heterogeneous disease group [14, 32], in which partly presynaptic, partly postsynaptic pathomechanism may have a role. Common characteristics are: It starts under two years of age with symptoms of ocular (local) muscle weakness only, the mothers of these infants are not myasthenic, no ACh-receptor antibodies can be found in the serum, drug resistance is considerable, and the result of thymectomy is very poor, if any [14].

In the Hungarian literature we have dealt with childhood MG in a few

studies [95, 96, 97, 98, 100, 101, 103, 104, 105, 106], concerning both the clinical and the pathological aspects. Special importance may be attributed to this question from a practical point of view, namely from that of modern therapy and surgery. Children and juvenile patients who undergo thymectomy on a proper indication and early, can recover or go into a very good remission, bordering on the healthy state. Our large casuistic diagnosed, observed, treated and followed-up according to the same and uniform points of view, provides a good opportunity to examine this complicated problem both from clinical (surgical) and pathological aspects.

Casuistic and Methods

Data of 1050 patients with MG (or myasthenic syndrome), examined, observed and treated between 1951 and 1987 were analyzed concerning incidence in childhood and adolescence. The age ranges for childhood and adolescence were determined to be 0—14 and 15—18 years, resp., following common Hungarian usage.

Transitory (neonatal) MG was diagnosed immediately after delivery of myasthenic mothers, if any myasthenic symptom was observed in the newborn.

Thymectomy was performed on a part of the patients. The operation technique used in every case was median sternotomy [109]. Operation took place without relaxation, in general anaesthesia through a tube. Tracheostomy was also performed together with sternotomy in the cases of bulbar or crisis-endangered MG. Preparation of the patients for thymectomy took place in our neurological departments; in the course of this, infections of the mouth, sinusitis were examined and treated, if necessary, tonsillectomy was performed in the case of chronic inflammation or when the tonsils were considered to be focal. All these procedures are necessary to avoid or to diminish the possible danger of mediastinitis [98, 103, 106, 109]. The patients spent 1—5 days in the intensive care unit (Dr Kertész, T.) where artificial respiration (IPPR) was applied, when necessary. In the first 24—48 h after surgery, no cholinergic drug was given to the patients ("postoperative drug withdrawal"). Suture removal was possible in general on the 13th day after surgery. Then the patients returned to the neurological department for short observation and for the new determination of drug dosage. The whole procedure: preparation of the patients, surgery, aftercare needed 25 days in cases without any complication.

Evaluation of thymic tissue concerning its activity, took place according to the number and size of thymic germinative centres, and was divided into three degrees of hyperplasia. When no germinative centre was present, histological diagnosis was persistent thymus [110].

For the registration, evaluation and follow-up of the patients' condition, a method was used which had been elaborated by one of us [99], and has been used for over a decade with benefit. In this system, called Disability Status Scale (DSS), we evaluate the patients' condition in six functional areas according to a point system, between 0 and 10. The higher the number, the worse the state of the patient. The six functional areas include all the characteristic symptoms of MG: there are ocular, facial, bulbar, sceletal, respiratory and other (autonomic, psychic) systems. The follow-up time is 6 months—15 years, (on average 6.7 years).

All the drugs and methods known in MG therapy were used in the treatment of the patients, but immunosuppressive cytostatic therapy and plasmapheresis.

In a part of the patients HLA-antigens were also determined, especially in familial cases [41, 107], and a family was reporded

in which three cases of manifest MG occurred in juvenile siblings and further four cases were found to have provocable MG [107].

Results

In this casuistic *113 cases* (10.76%) with childhood MG, and *96 instances* (9.14%) with adolescent MG were found, in total *209 patients*, 19.9% of the whole patient material of *1050 cases*. Those adult patients whose myasthenic symptoms started (possibly) in their younger age, were not included in this statistic. The number of the girls and that of boys in the childhood group are 69 (61.1%) and 44 (38.9%), resp., while among the adolescent patients 56 (58.3%) and 40 (41.6%), resp. The average age: 9.9 years ($\sigma = 3.58$) and 16.1 years ($\sigma = 0.89$), resp.

Neonatal (transitory) MG occurred in 5 cases out of 113 (4.42%), in 3 girls and 2 boys. In these cases the mothers suffered from MG in every case. In one instance, the recognition of the newborn infant's MG led to diagnosis of the mother. In another case a myasthenic mother gave life to two children with transitory MG. The first baby was born prior to her thymectomy, the second one after it. This case proves quite conclusively, that neonatal MG depends neither on the operation of the mother, nor on her remission state. Transitory MG lasted from 6 days to 3 weeks, in one case to 6 weeks. In all cases careful observation, feeding and drug therapy was necessary, but no artificial respiration had to be used. All the children who were born with neonatal MG, became healthy later on, no problem or trouble occurred in their development.

Congenital local, non-progressive MG occurred in 46 cases (40.7%) in the childhood group, and in only 5 cases (5.2%) in the adolescence. These cases belonged to the ocular group, all the same mild bulbar and sceletal alterations were also observed in one-third of the cases. By EMG-record we could observe the typical decrementum in amplitude, furthermore in two cases velo-palatinal EMG-examination (Dr. Horváth, Sz.) showed alteration of the bulbar musculature.

MG simulating brain-stem process, a form which had been described by us elsewhere [108], occurred in 14 instances (12.4%) in the childhood casuistic, but none in the adolescence. This special form of MG occurs neither in adults, nor in small children; it can be considered specific and exclusive to the age range of 10—14 years.

As a *new form of MG*, we mention 9 cases (7.9%) of the congenital childhood group. These children started as having common congenital MG, with ocular symptoms only. At their age of 8—12 years, however, the course of the disease changed, it became progressive and generalized with facial, bulbar and sceletal symptoms. So this MG turned into a form similar to that found in adults. According to this change, the whole therapeutic plan had to be changed and thymectomy had also to be performed.

The other 39 cases (34.5%) of MG in childhood and the majority of the

adolescent cases were similar to or identical with adult age MG. In these groups the generalized symptoms were predominant with fluctuation in a day, so characteristic to MG. The electrophysiological findings and the efficacy of the cholinergic drugs were also similar to that in adult, acquired MG.

Thymectomy was performed in 39 instances (34.5%) in the childhood group, and in 72 cases (75%) in adolescence. The significant and very good results of surgery are shown in Figs 1 and 2. As it can be seen, the majority of both groups have either fully recovered or significantly improved. Expressing the results in our DSS system: the average point value in the childhood group was 5.46 ($\sigma = 1.28$) before surgery and 1.75 ($\sigma = 2.79$) after it, while in the adolescent group 5.54 ($\sigma = 1.54$) and 2.16 ($\sigma = 2.32$), resp. The degree in both groups is mathematically significant ($p < 0.001$). In the group of childhood cases we had two fatal cases: an 8-year-old boy, who had

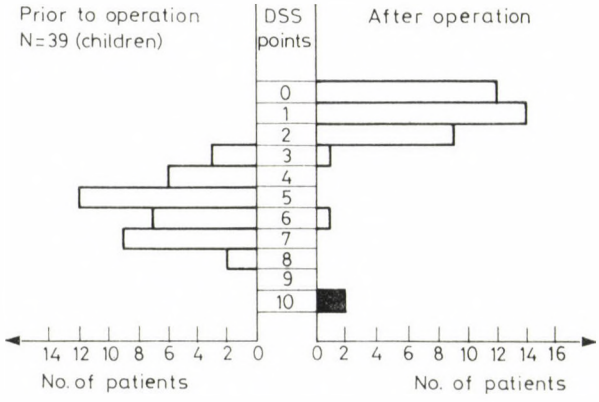

FIG. 1. Result of surgery in childhood MG expressed in DSS-system

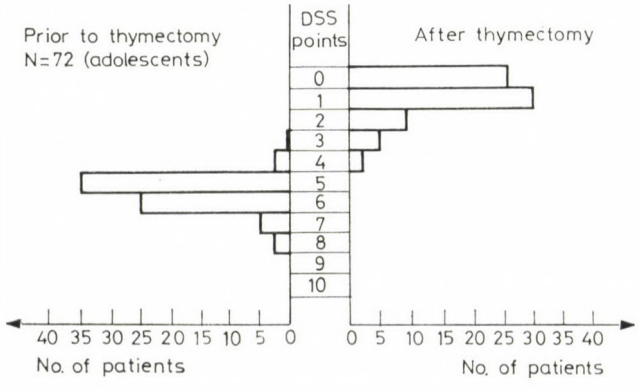

FIG. 2. Result of surgery in adolescence MG expressed in DSS-system

thymoma (darkcell epithelioma with minimal lymphoid reaction), died 4 months after surgery. Another boy (9 years old) died in postoperative myasthenic crisis. In the course of surgery, tracheotomy was performed in 8 cases (20.5%), and 17 cases (23.6%) resp., on account of bulbar or brain-stem MG or in crisis-endangered cases. In one case, maintenence of the stome and tube was necessary for a very long period.

The *histological examination* of the thymus gland showed in the majority of the cases a strong activity reflected in germinative centres, and was considered to be hyperplasia III or II [110]. No non-active, persistent thymus was found in either groups. In addition to the childhood tumour mentioned above, one further tumour was found in the adolescent group: a nut-size epithelioma with marked lymphatic reaction of a 15-year-old girl.

X-*ray irradiation* of the thymus gland can be performed also in childhood [38, 100, 103, 105, 106]. We tried to use this therapy in a few cases of congenital MG, too, but without convincing results, while the efficacy of radiation therapy agreed with that in adult MG (Dr. Rakonczai, G.).

Drug therapy of juvenile patients is identical with that of the adult form. Neonatal and generalized MG in childhood react in general quite well to drug therapy, while congenital MG proved to be resistant as mentioned above. The basic drug in childhood MG is pyridostigmine (Mestinon) in general, sometimes combined with ambenonium chloride (Mytelase). There are very few cases in which neostigmine (Prostigmin, Stigmosan, Neostigmin) seems to be indicated. In the ocular congenital form, relatively favourable effect can be achieved by alternate-day prednisolon in some cases, resistance, however, is a disadvantage in the majority of these children. Potassium salt may be useful as adjuvant drug also in childhood MG, as it does vitamin E in restricted dosage.

Based on literature and on our large casuistic, we propose the following *classification for childhood and adolescent MG:*

1. *Neonatal (transitory) MG:* Mother is in every case myasthenic, the symptoms of the newborn disappear within 6 weeks. Drug treatment is necessary, respiratory crisis may occur, therefore recognition of this form is considered to be life-saving. These children will not be myasthenic in later life, neither will their children. Their somatic and psychic development are normal. The supposed cause of this form can be the transient occurrence of ACh-receptor antibodies in the babies of maternal origin (via placenta).

2. *Congenital MG.* This form can manifest itself after birth or within 2—3 years of life. Symptoms are local, ocular (or oculo-sceletal); a non-progressive form, in which no AChR-antibodies can be found. Later on it can turn in to the "burned out" state. The mother is not myasthenic but the familial character is stressed, (sometimes reflected also in the HLA antigen status). There are multifold pathomechanisms in this form [23, 24, 25, 26, 27, 28, 29, 30, 44, 14, 32, 113], and also manyfold developmental anomalies can occur (with mental retardation, too).

3. *Congenital MG with late generalized symptoms.* Beginning and initial symptoms are similar to that of the former group, but the clinical picture changes when the child reaches the

age of 7—12 years: it becomes progressive, generalized, having facial, bulbar and sceletal symptoms, and it becomes similar to adult, generalized MG. This form of MG has not been described in the literature hithertoo.

4. *MG simulating brain-stem process* [108]. This form manifests itself at age of 10—14 years, with hardly fluctuating ocular symptoms which will be complemented soon by bulbar and sceletal symptoms and with inclination to respiratory crisis. Effects of the cholinergic drugs are poor, the result of thymectomy is still beneficial. The patients tend to full recovery.

5. *Childhood MG* at any age under 14 years, with generalized symptoms symptom-fluctuation has a very, good tendency and chance to recovery after thymectomy.

6. *Adolescent (juvenile type) MG* is identical with the adult acquired MG, with excellent benefit from thymectomy.

7. *Associative MG, myasthenic syndrome or reaction.* It can appear at any age in children or adolescents associated with other disorders, mainly with immunopathies, immunodeficiencies, myopathies, vasculitis, polymyositis or toxic conditions. It has an inclination to spontaneous remission, or improves well under steroid treatment.

Discussion

We may state that the clinical problems of childhood and adolescent MG figure rather scarcely in the very large amount of literature, dealing with the theoretical questions of the disease. So the analysis of great casuistics can contribute to the question which is more important from a practical point of view, than the theoretical discussions containing not infrequently contradictory data. We may suppose that publication of our casuistic, which represents one of the largest patient materials of the literature, may shed light on some problems of childhood and juvenile MG.

Swift [94] summarises the heterogeneous procedures which can lead to a neuro-muscular block. He attributes great importance to MG or/and different myasthenic syndromes in the series of these procedures. We also have dealt quite a few times with the model disease character of MG [96, 100, 101, 102, 103, 104, 105, 109]: MG is a disease in which disorder of neuro-muscular stimulus transmission can be studied best; in which the autoimmune pathomechanism has been proved, furthermore both the target-organ (striated muscle), and the antigen, (AChR protein alfa-subunit) are known. Likewise, the secondary morphological and biochemical alterations of the synaptic area, originating from the autoimmune mechanism, are well known [17, 18, 19, 20, 21, 23, 24, 25, 26, 27, 28, 29, 30, 31, 53, 54], and could be fitted in well with autoimmune view of the disease. Knowing the autoimmune mechanism, one can well understand the transitory MG. ACh-receptor antibodies can be found in the serum both of the mother and newborn [63], furthermore in the

amniotic fluid, too. The clinical condition of the newborn improves parallel with the successive decrease of the antibodies [2, 7, 15, 22, 50, 51, 70], and transitory MG expires, in general, within 3—4 weeks. Prolonged neonatal MG was observed only in one infant [10]. In one case neonatal MG lasted for 6 weeks. The severity of neonatal MG is independent of that of the mother. The maternal antibodies hardly correlate with the newborn MG [7], the babies do not produce antibodies, their disease is dependent on the maternal antibodies. So it is clearly understandable that these children do not develop MG in later life.

Ratio of transitory MG is just about 8—12% in the literature [14, 48, 49, 51, 52, 59, 116], while in our casuistic significantly lower. The reason for that cannot be other, than careful therapeutic plan, aftercare, planning of the pregnancy and delivery (Dr. Szeker, J.).

Drug treatment is sufficient in general for the therapy of neonatal MG. In one case plasmapheresis was necessary [16]. Respiratory crisis is relatively rare [40, 55, 58, 66, 111], it did not occur in our cases. The neonatal (transitory) MG is important from a theoretical point of view, because it allows conclusions to be drawn concerning the pathomechanism. Still it is more important in the practice, because its recognition may decide the lot of the patient.

It is beyond any doubt that the question of congenital MG can be considered to be the most important one among the theoretical problems of MG. We discussed its characteristics, and it is quite appearent from this that this form differs substantially from adult, acquired MG. Only clinical manifestations are similar, the ways of pathomechanism are very different, manyfold, sometimes presynaptic [25, 26, 27, 29, 30, 44, 62, 113, 114]. In spite of the very detailed studies concerning this form of MG, no case has been described similar to our 9 cases: namely typical and stationary cases of congenital MG, with only ocular symptoms for years, which changed and progressed into a generalized form at the age of 8—12 years. This form has been unknown so far even to such an outstanding expert of this problem, as Gomez [39]. So in these cases the possibility arises that this subspecies may be related to some geographic or HLA-antigen factors which have not been studied hitherto. In this new form of congenital MG the therapeutic plan has also to be changed parallel with the progression and generalization of the disease. This means that in these cases thymectomy may also be considered, as it happened in some of our cases with benefit [109].

MG simulating brain-stem process was first observed and described by us [108]. Later on further cases became known [6, 33]. This form, characteristics of which were mentioned before, is rather rare. Its importance can be seen in the fact that the patients are usually admitted first to a neurosurgical department on account of their misleading symptoms, and the

customary examinations are partly burdening, partly time-consuming for the patients.

We separated the childhood MG cases from the adolescent ones, while in other casuistics these cases are discussed together (Tabl. I). So the ratio of these two age-groups cannot be determined. This latter form is similar to MG in adult age, so are its therapeutic results, too. In these cases the indication for thymectomy is quite evident, if the conditions of the surgery are present. The results are unequivocally excellent (Figs 1, 2). The average age of the patients ranges from 7 years to 9 years [92, 74]. It was 9.9 years in our casuistic. It is interesting that some peaks of ages can be recognized: so in the great casuistic of Snead et al. [92] the 2—4., 12 and 16—17-year age ranges, in our one the 2—3., 7—9 and 11—13-year ranges [105]. In other casuistics this special grouping does not figure, or at least is not mentioned. It is not known, whether biological or only statistical phenomenon is reflected in this fact.

Rodriguez et al. [84] report on 2.24% spontaneous remission in comparison to 26% remission after thymectomy. In other great casuistics postoperative remission was much higher (Table I), in our casuistic also very good (Figs 1, 2). Results achieved in the adolescent group do not differ, if at all, from that in young adult MG.

Correlation of the activity of the thymic gland and the benefit of thymectomy is quite apparent in this casuistic, too, resembling our experience in adult patients with MG [109, 110]: The more active the exstirpated thymus (reflected in germinative centres), the better the result of thymectomy. The opposite standpoint [76, 77] can be rejected quite sharply on the basis of the observation in this casuistic, too. The very good results of surgery in the juvenile groups, can be explained by the very fact that the thymus exstirpated by sternotomy was very active, showed hyperplasia of degree III or II in almost every case.

Indication of thymectomy can be considered to be evident from the previous facts: No thymectomy has to be performed in congenital local (ocular) MG, all the contrary, however, all the myasthenic patients of juvenile age need to be operated, if the conditions are given, and a myasthenic reaction can be excluded by the timefactor and by other characteristics. The same applies also to MG simulating brain-stem process, and to those congenital MG cases, in which generalized symptoms, bulbar symptoms or respiratory crisis develop. We consider the age of 7 years to be the lowest age limit for thymectomy, in order to avoid the possible occurrence of DiGeorge's-syndrome, (sometimes called in the literature wasting-syndrome).

Congenital MG cases with familial involvement are of special interest [32, 34, 40, 49, 82, 84]. There are a few cases in which monozygotic twins became myasthenic [4, 46, 65, 73], in another case one twin [5], yet in

another one three cousins [75]. Namba et al. [66, 67] raised the possible role of genetic factors already in 1971: in 6 cases both twins, in 15 cases only one twin were sick. MG has not been described on multifold twins. Respiratory crisis was observed in familial cases in a few instances [13, 58, 114]. There are only three cases which have been followed until adult life [37]. In our casuistic we can report on two twin-pairs with MG, and a family, where three sisters became myasthenic at an early age. No respiratory crisis occurred. One twin-pair has been observed till now, into adult life.

Myasthenia-like syndrome can occur in association or combination with other diseases. The ratio of association of adult MG with immunological disorders or syndromes is about 15% [102], this ratio, however, has not been clarified concerning childhood MG. There are data showing very high association ratio (92), but the association of some disorders can be considered to be coincidental only. MG and epilepsy or myasthenic syndrome provoked by anti-epileptic drugs (trimethadione, hydantoin derivates), was reported in a few cases [8, 47, 69, 78, 80]. In our casuistic, we found only one case in which myasthenic reaction caused by hydantoin therapy could be considered [119].

Thymoma is extremely rare in childhood [12, 43, 67]; in our patient material one tumour was observed in childhood and another one in adolescence (epitheliomas with minimal or marked lymphatic reaction). Association of MG and myopathy is quite common in childhood. At such occasions the combined disorder can be considered to be myasthenia myopathica, or myopathia myasthenica, depending on which component is predominant or more emphatic [96, 100, 102, 103, 104, 105]. Familial limb girdle MG [11, 32, 60] could probably be considered as a mistake, and could be classified among myopathies; this can be supported by the presence of tubular "aggregations" [11]. We observed and described megaconial and pleioconial mitochondria in pure MG [54], these peculiar mitochondria thus are not suitable to differentiate independent myopathy, all the more as they can occur in normal muscle, too [79].

There are some very special and rare associations in the literature: one myasthenic syndrome with leukaemia [90], another one together with neuroblastoma of the chest [83], two instances with SLE [42, 117], one case with rheumatoid arthritis [1], and one case after bone-marrow transplantation [91]. In our casuistic, one case deserves to be mentioned: agammaglobulinaemia discovered in a 4-year-old girl was followed 8 years later by a very severe, crisis-endangered MG (not a syndrome).

As we can see, MG in childhood and adolescence cannot be considered to be rare. The two groups together add up to a ratio of 20% of all cases with MG. The establishment of the diagnosis and the elaboration of the therapeutic plan demand more

carefulness in childhood than in adult age, on account of the heterogeneous groups, genetical factors and different clinical manifestations. In a considerable part of the cases healing can be achieved by proper therapeutic methods. Other cases need to be follow-up constantly, because of the possible change of the disease-course.

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