MYASTHENIA GRAVIS IN CHILDREN

BY

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Since its recognition as a clinical entity by Wilks in 1877 and Erb in 1879, myasthenia gravis has been considered a rare condition in children. The commonest age of onset is in the third decade, with a higher incidence in women than in men. Early collections of case records mentioned few patients affected before the tenth year. Palmer (1908) from an eight-year period collected 126 records; in five cases only the onset was under 20 years, the earliest being at 2 years of age. Gerstle (1929), among 67 case reports from the National Hospital, Queen Square, London, in the period 1900 to 1927, found two cases under 10 years, the youngest being a child of 6. In a more recent survey directed to the younger age groups Levethan, Fried, and Madonick (1941) reported a total of 34 cases under 17 years of age, of which only eight were less than 10 years old.

Where full case histories, however, are available, it is sometimes clear that the disease has been present since infancy. No doubt in the past, before the use of prostigmin, cases in infants, in which ocular and other cranial nerve palsies are so common, were wrongly diagnosed as nuclear ophthalmoplegia and nuclear aplasia of the von Moebius type. Within the last decade notably, the reports of cases in infants and young children have been growing steadily, largely due to the facility of observing the response to a diagnostic injection of prostigmin. An interesting point on the mortality of the disease, before the beneficial effects of eserine and physostigmin were observed by Walker (1934), is that in collections of cases observed covering several years, Palmer stated that of 126 cases 50 were known to have ended fatally. In Kennedy and Moersch's (1937) 87 cases of the period 1915 to 1932, 34 had died. Such figures should be kept in mind when considering the advantages of modern therapy with prostigmin or thymectomy, without denying the benefit obtained by their use in alleviating symptoms and prolonging life.

The disease is said to be non-familial, though many exceptions have been recorded. Hart (1927) and others have described its occurrence in sisters, Bowman (1948) in boy and girl cousins, with onset

at the ages of 3 and 4 years. A remarkable family incidence is recorded by Rothbart (1937) of five brothers affected since infancy, of whom one died at 7 months of pneumonia, the ages of the others being 9, 13, 15, and 18 years. A sister and both parents were unaffected.

Intrauterine influences in myasthenic mothers are held to account for some babies being born with symptoms of myasthenia, who, surviving the neonatal period, may lose all signs of the affection even in the absence of treatment. Such an infant, recorded by Strickroot, Schaeffer, and Bergo (1942), died on the third day, while Wilson and Stoner (1944) mention two affected children of a myasthenic mother, one dying on the fourth day, and the second without treatment becoming normal by the age of 9 months. An earlier pregnancy, before the mother developed myasthenia at the age of 25, had resulted in a normal infant. A similar example is that of Stone and Rider (1949), where the myasthenic baby was relieved by prostigmin, but continued to improve without further treatment. In such cases the weakness was chiefly one of feebleness in crying, sucking, swallowing, without ocular palsies. Conversely, many cases have been recorded of infants with signs of myasthenia at birth, whose parents have both been unaffected. In these cases, as in others of later onset, ocular palsies, especially ptosis, are the salient features with, in addition, general weakness and difficulty in swallowing and sucking. Levin (1949) reviewing these congenital cases describes the conditions in twins, and suspects a genetic origin. Both children, a boy and a girl, were stated to have had feeble antenatal movements, and at birth had a weak cry, difficulty in sucking and swallowing, and limited ocular movements and ptosis. One child died of pneumonia at about 4 years of age despite prostigmin therapy, and the other had improved considerably by the seventh year. Levin states that the mother had two first cousins, both girls, with congenital bilateral ptosis, one of whom died in her eighteenth year. Against the genetic theory is a severely affected patient of Wilson and Stoner (1944), who had an unaffected uniovular twin.

The four cases we have to describe were all in girls, with signs of myasthenia first appearing at the ages of 2, $3\frac{1}{4}$, $3\frac{1}{2}$, and 10 years. The parents and siblings were unaffected.

The symptoms of myasthenia gravis are so well known that a full description is not necessary. The characteristics are fatiguability, weakness, and possibly paralysis of striated muscles, with a remarkable tendency to remissions and relapses. At all ages, but especially in children, cranial nerve muscles are affected first, the most obvious being ocular symptoms, bilateral more often than unilateral ptosis, and restricted movements of the eyes.

Levetan and his colleagues estimate that ocular symptoms are among the earliest in over 70% of cases. Pupillary paralysis has been recorded, but is extremely rare. Disturbance of speech, mastication, swallowing and respiration quickly call attention to themselves. While ocular pareses are frequently permanent though of variable severity, difficulty in swallowing and breathing are commonest during exacerbations, and of course are the most dangerous of all the symptoms, often coming on suddenly and being unaffected even by large doses of prostigmin. The type of onset, except the congenital cases, is usually gradual, but may be fulminating, as in a negro boy of 7 years described by Lieberman (1942). Upper respiratory infections have been mentioned as preceding the appearance of symptoms. Any infant or child with signs of cranial nerve palsies, especially ocular paralyse, ptosis, weakness in speaking, coughing or crying, lack of facial expression, the ironed-out look, should be given a test injection of prostigmin, 0.1 mg. subcutaneously. Marked temporary improvement will always occur in myasthenia gravis. Another feature worth looking for is the retention of the tendon reflexes despite the weakness and fatiguability of the muscles.

In a condition noted for its remissions and relapses, it is impossible to give a prognosis in children, as in them the mortality is greater, and the period of survival often shorter, than in cases of later onset. In Levetan's survey of 34 cases under 17 years of age (Levetan *et al.*, 1941), the average duration of observation was 46 months, 10 having had a fatal termination within an average of $15\frac{1}{2}$ months. We have observed in two of our cases that, in a severe relapse, difficulties in swallowing and in breathing proved unresponsive to high doses of prostigmin, though during remissions the return to a normal state of the muscles was complete in one. In the other, only minor ocular paresis persisted. These remissions were unaffected by the absence of prostigmin dosage through forgetfulness at home, or a delay in the renewal of the prescription.

Case Reports

Case 1. A girl, born March 1, 1940, was first admitted to The Hospital for Sick Children on November 16, 1943, aged 3 years 8 months. The history was that she had been perfectly well up to six weeks before admission, when she had a mild attack of tonsillitis. This cleared up, but the child seemed to be talking thickly. Five days before admission, her mother noticed that the child had bilateral ptosis. She also had an unproductive cough and some difficulty in swallowing.

On examination, her speech was slurred, and her face immobile. There was marked ptosis of both eyelids. The pupils reacted to light and accommodation. There was slight nystagmus. The palate and facial muscles moved poorly. Lumbar puncture revealed no abnormalities. During her stay in hospital, up to December 29, 1943, there was a marked improvement of all signs.

There was a recurrence of the ptosis early in September, 1944, but she remained well until April, 1946, when she had her tonsils and adenoids removed, and caught scarlet fever. After this time she became very nervous and easily frightened. There was no ptosis, but very slight nystagmus looking to the left. The third incident of aggravation of the disease, the previous two having occurred in November, 1943, and September, 1944, occurred in June, 1948. She was seen again in the Out-Patient Department and she showed marked ptosis, difficulty with close vision, a thick speech, and she complained that her legs ached. Her face was expressionless, and her mouth sagged. There were no abnormalities in the other cranial nerves. She was readmitted to hospital and gave the following history: four days before admission, after doing fine needlework at school, she complained of difficulty in seeing small stitches. The next day, a drooping of the eyelids was noticed. The day before admission this was more marked. Her voice was very thick and she could not pronounce certain words. Her appetite was good, but on eating she tired towards the end of a meal.

On examination, the speech was toneless and became slurred after counting up to 30 or 40.

An examination of the cranial nerves (third, fourth, and sixth) revealed that she could not read small type; that there was a slight internal strabismus; that the convergence was very weak, and that there was a bilateral ptosis. An examination of the fifth nerve showed that the masseters were weak: the spatula held between the teeth was easily withdrawn. An examination of the seventh nerve showed that the facial movements were very limited. The girl had a sad appearance, she could not smile, or wrinkle her forehead on looking upwards. An examination of the ninth and tenth nerves showed that the elevation of the palate was poor.

No other abnormalities of the central nervous system were found. The power of limbs and trunk was normal. Other systems were also normal.

In the radiograph of the chest, no thymic enlargement was detected. The Mantoux reaction was negative at 1/10,000.

All the girl's muscles responded to short duration stimuli, but tired rapidly, especially the small muscles

of the hands. The response to prostigmin, 0.25 mg., followed by a further 0.25 mg., given subcutaneously, produced a good recovery of the facial muscles.

Progress. On June 10, 1948, administration of tetra-ethyl-pyro-phosphate, 1 mg. t.d.s., was begun, and increased to 2.5 mg. without any favourable response.

On June 12, 1948, prostigmin, 5 mg. by mouth, t.d.s., was begun with definite improvement.

On June 30, 1948, the dosage of prostigmin was raised to 10 mg. t.d.s. with further improvement. The only residual defect was very slight ptosis. She was discharged on July 1, 1948.

When she was treated with prostigmin, 10 mg. b.d., the slight ptosis and facial weakness were most marked in the evenings; otherwise she progressed very well.

The fifth admission was on January 12, 1949. The recent complaint was that two days before admission, the child had a cold. She developed a cough and complained of abdominal pain. On the day of admission there was acute respiratory distress. The child was cyanosed and delirious.

On admission, there was pneumonia in the right lower lobe. She was treated with penicillin and sulphadiazine. After several attacks of acute dyspnoea, the chest

FIG. 1.—Photograph of Case 1 showing expressionless face.

FIG. 2.—Case 1, smiling.

The fourth admission was on October 27, 1948, and she was discharged on November 5, 1948.

She remained in her usual condition on prostigmin until one week before admission, when ptosis became worse, and she had some difficulty in chewing and swallowing. Her voice was thick, and her legs became tired after exercise, particularly at the end of the day. The dosage of prostigmin was trebled with some improvement.

On examination there was seen to be bilateral ptosis, and poor convergence with slight nystagmus. There was an obvious facial weakness, but otherwise no clinical abnormality.

condition cleared by January 20, 1949. During the acute illness, she had prostigmin, 1 mg. subcutaneously, two-hourly, and guanidine hydrochloride, 80 mg., four times a day.

On January 21, 1949, the prostigmin was reduced to 1 mg. three-hourly, and on January 29 she had four-hourly injections at night. By February 3, she missed out the 2 a.m. injection, and on February 6, she started four-hourly injections by day. She did not do well on this, however, and she reverted to three-hourly injections by day. Guanidine hydrochloride did not seem to be having much effect and it was stopped on February 9, 1949.

The sixth admission was on May 27, 1949, and the usual symptoms of ptosis and facial weakness were present.

During her stay, it was found necessary to increase her prostigmin to 15 mg. orally, four times a day.

She was seen once monthly in the Out-patient Department and had been very well up to February, 1950, when there was evidence of facial weakness again. She was taking prostigmin, 15 mg. orally, three times a day.

In April, 1950, there was a slight orbicularis palpebrarum weakness. Afterwards she remained well until early in October, 1950, when she had a head cold for

Respirations were 26 at 10 a.m., when bilateral basal congestion of the lungs with patchy collapse was diagnosed.

She was treated with postural drainage and sulphamezathine, and an increase in prostigmin, 1 mg. three-hourly, subcutaneously. The white blood count was 18,000 per c.mm. She appeared well, ate lunch normally, until 2 p.m., when an attempt was made to give her a dose of sulphamezathine. The patient appeared to have difficulty in swallowing, and became acutely distressed with cyanosis and difficulty in breathing. Despite prostigmin, oxygen, and artificial respiration, there was

FIG. 3.—Photograph of Case 2 showing ptosis and expressionless face. (Aged 6 years.)

FIG. 4.—Photograph of Case 2, aged 9 years, showing unilateral ptosis.

one week, but was not incapacitated. She was on prostigmin, 15 mg. twice daily.

On October 30, 1950, the ptosis was marked, and therefore an injection of prostigmin, 0.5 mg., was given.

The seventh admission to hospital was on November 4, 1950. Her speech was thick; there was ptosis, and the right eye deviated upwards and outwards. There was no cyanosis. She was able to swallow normally.

On November 7, 1950, prostigmin by subcutaneous injection was given eight-hourly, as ptosis and facial weakness persisted.

On November 8, 1950, for two short periods, she had difficulty in swallowing, and increased ptosis responded rapidly to injections of prostigmin.

On November 9, 1950, her temperature was 100° F.

no response, and the child died of respiratory failure at 2.15 p.m.

Case 2. A girl, born on July 9, 1941, was admitted to The Hospital for Sick Children on October 11, 1945, with the following history. One year previously, she developed ptosis of her left eye, and three months later her right eye became similarly affected. Five months after this, the left side of her mouth began to droop, and her face tended to become expressionless, although from time to time improvement was noted. Six weeks before admission, she started tripping and fell on several occasions. Since this time she had seemed off colour and tired very easily, although half an hour's rest was sufficient to restore her strength temporarily. On one occasion she was said to have collapsed suddenly, and

attempted to cough up some stringy mucus. Twenty-four hours before admission her breathing became abdominal and she became collapsed.

On examination, she was found to be white and collapsed. Her chest was full of moist râles, and there was practically no movement of the intercostal muscles.

With this history, she was thought to have myasthenia gravis, and was given an injection of prostigmin hydrochloride 0.25 mg. and atropine sulph. 1/150 gr., subcutaneously. Within five minutes her breathing deepened and she attempted to cough up stringy mucus.

The subcutaneous dosage of prostigmin was changed to oral doses of 60 mg. four-hourly, later reduced to 45 mg., 15 mg., and finally was omitted for 48 hours. At the end of this period she was able to walk up and down six floors of the hospital without tiring, although the expansion of her chest was only 1 in., and she still had ptosis. Three weeks after admission, she was operated on by Mr. Geoffrey Keynes and the thymus was removed. Pre-operatively, she was given 5 mg. prostigmin orally, on three occasions, at six-hourly intervals, and three hours after the last of these, she was given 1 mg. subcutaneously. Post-operatively, she was treated with

FIG. 5.—Photograph of Case 3 before prostigmin.

A few hours later, however, she once again collapsed, and her breathing became very shallow and solely abdominal. Also she became severely cyanosed. She was, therefore, put into a Drinker respirator, and an improvement in her colour was apparent after a very short time. She was again given 0.5 mg. prostigmin and 1/150 gr. atropine. This dose was increased to 0.75 mg. prostigmin and 1/150 gr. atropine six-hourly, but there was not much response to therapy, and she had a cyanotic attack during the night.

Next day, 1 mg. prostigmin, four-hourly, was prescribed, and in the evening a sudden improvement was noted. For the next three weeks her condition tended to improve. The periods in the Drinker apparatus became shorter, and 14 days after she had been put in it, she was able to do without it.

FIG. 6.—Photograph of Case 3 half-an-hour after receiving 0.5 mg. prostigmin subcutaneously.

prostigmin 0.5 mg. and atropine 1/150 gr., four-hourly, subcutaneously.

On coming round from the anaesthetic, her eyes were seen to be wide open, although the ocular improvement was still poor. Twenty-four hours post-operatively, the injection of prostigmin was changed to oral administration of 30 mg. four-hourly, and next day to 15 mg. four-hourly.

Ptosis returned about one week following operation, and ocular movements, which had been about half the full range, became more restricted. It was noticed that her eyes seemed to be open widely in the mornings, but ptosis set in after a few hours.

The child was discharged a fortnight after operation. For the last six years she has been observed in the Out-patient Department, and on the whole her general condition has been good. She has been maintained on a dose

of prostigmin varying between 5 to 10 mg. orally, t.d.s. Her ocular movements have varied between ophthalmoplegia and full movements; her pupils react to light and accommodation. Her ptosis has been most marked in the evening, and is more noticeable in the left eye than in the right; otherwise, she has been fully active and plays her part in normal school life. In 1951, her ocular symptoms were practically normal, but following a cold, there was sudden ptosis of the left eye, which gradually cleared up.

Case 3. A girl, born on September 29, 1940, was admitted to St. Richard's Hospital, Chichester, on November 25, 1950. Two months before admission she had a bad head cold. Six weeks before admission, she tripped and fell two or three times, and had difficulty in focussing her eyes while reading. Next day she felt weak, and had diplopia. Her eyelids felt heavy. Her mother noticed that towards evening her eyelids would droop, the corners of her mouth sag, and that by next morning these signs had disappeared. At this time she complained of becoming tired when chewing, and of having difficulty in swallowing.

On examination, she was a flabby, tired looking child, very hypotonic, and breathing rapidly and shallowly, mainly with the diaphragm. The hypotonia was increased by exercise. The only abnormal neurological sign was weakness of the external rectus muscle of the left eye.

Half an hour after an injection of 0.5 mg. of prostigmin intramuscularly the muscles regained strength and the eye movements became full. In the ward, prostigmin was withheld for a time, and the weakness seemed variable, although never entirely absent. Later, she was given 15 mg., t.d.s., by mouth and improved on this regime. After a fortnight the drug was stopped and no ill effect was noticed, as she seemed to be having a remission. She was transferred to St. Bartholomew's Hospital, London, and the thymus was removed by Mr. Geoffrey Keynes. Post-operatively, she was given 7.5 mg. prostigmin, orally, four-hourly, for one week, after which the drug was stopped. Since then she has remained well, and had no symptoms.

Case 4. A girl, born on June 14, 1943, was admitted to The Hospital for Sick Children on October 15, 1945. There is one other child, which is normal. Her previous history shows that her milestones were normal; she talked at one year. Her general health had been good until five weeks before admission, when her left eye drooped, and the left side of her face seemed to sag. Two weeks before admission, her left leg had been giving way when she was tired, and she had had frequent falls. One week before admission, her speech seemed increasingly nasal, and she had had difficulty in swallowing.

On admission, she was found to have slight drooping of the left eyelid, and slight weakness of the left corner of the mouth. The fundi were normal, and the pupils reacted to light. She had no nystagmus, but the ocular movements were restricted. The palate moved normally, and the tongue protruded in the midline. The power in legs and arms seemed normal.

More detailed examination of the eyes the day after admission revealed that, on looking to the left, the right eye turned three-quarters to the left, and the left eye

remained central. On looking to the right, the left eye turned three-quarters in the direction of the right, and the right eye did not pass the fixation line. Neither eye could rise above the midline, and they were unable to converge. There was slight palatal weakness, although palatal sensation was normal.

During the next few days, with the exception of the eyes, her general condition improved, and she was sent to convalescence. Here she continued to improve; the left eye was able to go past the midline on looking to the left, and she was able to smile a little.

Fourteen days later, however, she suddenly became very cyanosed. Artificial respiration was resorted to, and milk and mucus poured out of her nose. Her chest was very bubbly, although no impairment of resonance was detected, and she was put on a tipping board. She was by now unconscious, although her colour had improved. Respiration was 48, and pulse 144. Within 24 hours her general condition was better, but she had ptosis of both eyelids and palatal paresis. Three days after this attack she was well again, the palatal palsy had disappeared, and the ptosis was less.

Next day she had another respiratory and cardiac crisis with choking and bringing up of much mucus. She was nursed flat, and given injections of strychnine and adrenalin twice daily. Over the following seven weeks she improved and seemed comparatively well, except for slight ptosis and left facial weakness, but a further attack of cyanosis with difficult breathing and cardiac weakness ensued, which cleared up fairly well during the next three days, only to relapse again three days later in a more acute and dangerous way.

She was readmitted to The Hospital for Sick Children with marked palatal paralysis, pallor of the face, and with cyanotic tinged lips. She was restless and semi-conscious, while clear mucoid discharge from the bronchi welled up and spilled out of her mouth. As she was in such a desperate and severely shocked state, a detailed examination was not proceeded with. Coarse and fine crepitations were found all over the chest. The pupils were widely dilated and equal, and showed a sluggish response to light. She had ptosis of both eyes; it was more marked on the left. All reflexes were present, and the discs were normal. There was left facial paresis. The foot of her bed was raised, which mechanically helped her condition, and she was given 1/150 gr. atropine before meals.

Next day, the child had improved, although the facial paralysis and ptosis still persisted. Her face was expressionless, although now and again she made an effort to smile. The ocular movements were non-existent. Her arms held the cot sides for a time, and, growing tired, would flop down. Similarly, her legs could only support her for a short time before giving way. She was being tube fed, and salivary mucus appeared in her mouth on occasions and dribbled over.

Half-an-hour after these findings, she was given an injection of 0.24 mg. prostigmin and 1/150 gr. atropine. After 10 minutes she gradually became more lively, and after 20 minutes her expression had returned, she was smiling with ease, and able to open her mouth wide to eat chocolate; in the eyes, the ptosis improved, she was

able to raise the lids, and there was a definite movement of the eye muscles. Swallowing was greatly improved; she had a very good clearing cough, which was not present before. Half-an-hour later she was able to eat and enjoy a large plateful of lunch. Twenty minutes later, she was, with help, able to walk round the ward. Five hours later, the improvement gradually declined, but was rapidly restored by a further injection of prostigmin. Subsequently, prostigmin treatment was continued and she was put on 10 mg. by mouth three-hourly. On February 5, 1946, she was very well on this maintenance dose. The chest was absolutely clear. On February 5,

Pathology

The association of hyperplasia of the thymus or tumours of the thymus with myasthenia gravis has been noted in several papers. Blalock, Mason, Morgan, and Riven (1939) summarized the literature on the thymus in myasthenia gravis up to 1939, and showed that of 110 patients who had come to operation or necropsy, 31 had tumours, and 22 had enlarged or persistent thymuses. Bratton (1949) found 11 tumours in 70 cases of thymectomy. The

FIG. 7.—Photographs of Case 4 before prostigmin, showing ptosis, facial weakness, open mouth, and drooling saliva.

FIG. 8.—After 0.25 mg. prostigmin given subcutaneously.

1946, she was operated on by Mr. Geoffrey Keynes. The thymus was easily found following a midline incision over the sternum, and removed. The gland was small and discrete, and weighed 5.5 g.

After a stormy convalescence she recovered, and was discharged home on a maintenance dose of prostigmin, 5 mg. four-hourly. She was followed up in the Out-patient Department, and the mother stated with assurance that the child's eyes were wide open in the mornings, but that the lids drooped later. In the afternoon her legs became tired and her face more mask-like.

She started a cold five days after her last out-patient attendance, and the eyes and mouth did not look as well as previously. Two days later, she brought up a lot of mucus and pus from the chest, and died suddenly.

remaining specimens were compared with suitable controls and found to be similar in weight, shape, and proportion of glandular tissue, and he suggested that the conception of persistent thymus in myasthenia gravis should be abandoned. He proceeded, however, to describe two microscopical features which he frequently found in his material: first, an increased number of cortical nodules with a denser concentration of lymphocytes both in the cortex and in the medulla, and secondly, the formation in the medulla of so-called 'germ centres'; the latter were found in 66% of the glands examined as against 2% of non-myasthenic control cases.

Bryan, McDonald, and Clagett (1948) reported 23 proved cases of myasthenia gravis, exclusive of thymoma, in which thymectomy was done. On the basis of a quantitative microscopical examination, they considered that the thymus was either normal or partly replaced by fat in 17 instances. Six glands were found to show lymphoid hyperplasia with the formation of germinal centres. Castleman and Norris (1949) found 10 examples of thymoma in a group of 35 cases of myasthenia gravis; 75% of the non-neoplastic thymuses showed infiltration of the medulla with lymphoid germinal centres.

It would appear that, whilst there are no constant pathological changes in the thymuses of patients with myasthenia gravis, a significant proportion of the cases show lymphoid hyperplasia of a variable degree; further, some cases of thymoma are difficult to differentiate from extreme hyperplasia, and in others, both changes are represented in the same gland. There is as yet no general agreement on the neoplastic nature of the 'thymoma' of myasthenia gravis which is composed of both epithelial and lymphocytic elements. It is tempting to suggest that the non-neoplastic thymic pathology is the effect of myasthenia gravis.

Since the pathological changes in children with myasthenia gravis have but rarely been reported it seemed to us worth while to describe the findings in our four cases even though the number is small.

Case 1: Necropsy Findings. The thymus was normal in weight (29 g.), size, and shape. Microscopically, there was no evidence of involution of the gland. The cortex showed a good cellular density and there was an 'overflow' of cortical lymphocytes (thymocytes) into the medulla where reticulum cells were inconspicuous. No germinal centres were observed.

The child died from an acute mononuclear tracheo-bronchitis and interstitial pneumonitis. Coagulase-positive *Staphylococcus aureus* was isolated from the mucoid secretion in the trachea.

No significant abnormalities were noted in the endocrine glands, in many blocks of muscle or in any other tissue examined.

Case 2: Description of Surgical Specimen. The thymus consisted of two separate lobes, measuring 12×2 cm. and 10×2 cm. in their maximum diameters. The combined weight was 17 g. The lobular pattern was normal. The cortical nodules were of very high cellular density but no germinal centres were found. Hassal's corpuscles were very large and degenerate and the medullary reticulum was well defined.

Case 3: Description of Surgical Specimen. Microscopical examination of the thymus revealed large, highly cellular cortical nodules as well as germinal centres. The gland weighed 18.5 g.

Case 4: Description of Surgical Specimen. The specimen of thymus weighed 5.5 g. and consisted of two lobes. Microscopical examination showed no evidence

of involution. The cortex was extremely cellular and the medullary foci simulated germinal centres. Necropsy, four months after thymectomy, showed, on opening the chest, a well formed thymus of 8.5×5 cm. maximum diameters and 15 g. weight. This, on microscopical examination, showed an obliteration of the cortico-medullary pattern due to diffuse infiltration of the medulla by lymphocytes (thymocytes). All the parts of the gland were of about the same moderately high cellular density. Only a few Hassal's corpuscles were noted.

The child died from an acute catarrhal tracheo-bronchitis with pulmonary emphysema and collapse. There were also old pleural adhesions over both lungs.

None of the other tissues examined, including muscles, endocrine glands, and central nervous system, showed any noteworthy changes.

The findings in the four cases of myasthenia gravis were assessed against an unselected series of 100 children coming to necropsy. The thymus showed involutionary changes of varying degree in more than 80%. Changes suggestive of lymphoid hyperplasia without germinal centres were found in five children.

Although the validity of any conclusions is limited by the small number of cases observed in childhood, the findings seem to support the conception of an association of lymphoid hyperplasia of the thymus with myasthenia gravis. The interesting observation of the rapid regeneration of hyperplastic glandular tissue four months after partial thymectomy, further suggests that the thymic changes are secondary to myasthenia.

Discussion

Theories of the Causation of Myasthenia Gravis. Some form of interference in neuromuscular transmission at the myoneural junction is the accepted cause of muscular weakness in myasthenia gravis. A deficiency or a too rapid breakdown of acetylcholine, the substance facilitating the passage of impulse at the motor end-plates, lacks confirmation. On normal muscle exhaustion prostigmin has no effect, and a similar want of response would be expected in myasthenia if a defective synthesis of acetylcholine were the primary cause (Wilson and Wright, 1936).

Recent studies by Wilson, Maw, and Geoghegan (1951) of the cholinesterase activity in normal subjects and in myasthenic patients indicate that in either case the mean values of pseudo-cholinesterase in the plasma and of true cholinesterase in the red cells do not differ significantly.

Walker (1938) and later Wilson and Stoner (1944) observed that by the exercise of one group of muscles an increase in the fatigability of an affected group of muscles at a distance could be produced. In addition, Wilson and Stoner found that the serum

of a myasthenic patient not under treatment, when applied to the isolated nerve-muscle preparations of a frog, produced a block in neuromuscular transmission. The possibility, therefore, exists of a curare-like substance in the blood of the myasthenic patient which opposes neuromuscular transmission, but which can be neutralized or inhibited by the action of prostigmin. Whether the defect lies in the motor nerve end-plate itself, or in the tissue fluids surrounding it, is still undecided.

The influence of the thymus on the disease is also uncertain. Viets (1950), in discussing the value of thymectomy for myasthenic patients, finds 'slight but definite indications that there is some relation between the thymus and myasthenia gravis.' The chief morbid anatomical feature is a lymphoid hyperplasia with germinal centre formation, a condition sometimes found in association with a thymoma. In many patients, on the other hand, the thymus has been found to be normal, and attempts to reproduce the symptoms of myasthenia by the injections of extracts of normal and abnormal glands have so far failed.

Treatment. In a disease so prone to remissions and relapses it is not easy to form an accurate assessment of different therapies. The results of medical and surgical treatment cannot be entirely separated, as no one would be so hardy as to deny the benefits of prostigmin to the surgically treated case.

In 155 thymectomies between February, 1942, and July, 1949, all in adults, Keynes (1950) claims complete or almost complete remission of symptoms in 65%, and considers that the shorter the myasthenic history, the better the results. In his series there were 11.6% of thymic tumours. Viets (1950), on the other hand, does not advocate thymectomy in mild cases, nor in those responding well to prostigmin, nor in patients who have wide swings of remission and relapse. In 36 patients, having thymectomy, in addition to irradiation in some, between 1941 and August, 1949, seven had thymomas, three surviving operation. In the 29 non-neoplastic cases, 25 survived thymectomy, seven being followed for five or more years, and 18 for less than five years. The ages of onset of symptoms in these two latter groups lay between 11 and 33 years.

Of the many drugs which lead to some relief of the symptoms of myasthenia, prostigmin remains by far the most effective. Viets estimates that 15 mg. prostigmin bromide by mouth is equivalent in effect to 0.5 mg. prostigmin methyl sulphate subcutaneously or intravenously. The effect of a subcutaneous injection begins after 10 minutes and lasts about four hours (Nevin, 1951). For the child

presenting any of the severer signs of the disease, 0.5 to 1.0 mg. prostigmin is given by injection and repeated as required. In milder phases of the disease or remissions, 5 to 15 mg. prostigmin by mouth, three or four times a day, suffices, the doses being aimed to precede periods of greater physical activity. It was, however, obvious in the small number of cases in children we present, that during remissions, even with a persistence of some degree of ptosis and ocular palsies, the giving or withholding of the drug had no apparent effect. In relapses the response is happily usually dramatic, but in a sudden severe relapse (Case 1) no response was obtained from injections, even several times repeated. Any child with myasthenia gravis should be under the constant supervision of the private doctor, as a relapse may be fulminant and rapidly fatal. Thymectomy was performed by Mr. Geoffrey Keynes in three of our cases. The operative mortality was nil. One child died suddenly in a relapse four months after operation. Two are in good health with minor symptoms at the time of writing.

Summary

Four cases of myasthenia gravis in childhood are described. Thymectomy was performed in three of them.

The pathology, diagnosis, and treatment of the condition are described and discussed.

We are indebted to Mr. Geoffrey Keynes for his interest in our cases, and to Dr. Guy Emmerson for permission to use Case 3. Thanks are also due to Mr. Derek Martin for the photographs.

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